THE ROLE OF CUMULATIVE ADVANTAGE/DISADVANTAGE IN DISPARITIES IN ALZHEIMER'S DISEASE RISK

by

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As members of the Dissertation Committee, we certify that we have read the dissertation prepared by *Rachel Peterson*, titled *The Role of Cumulative Advantage/Disadvantage in Disparities in Alzheimer's Disease Risk,* and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

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DEDICATION

For Cree, Shayli, Kavan, Aya and Anneliese.

Never stop working toward your dreams.

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ABSTRACT

BACKGROUND: Substantial disparities have been observed in Alzheimer's disease (AD) by race and social class. The persistence of health disparities over time and for diseases with distinct etiological processes suggests that the fundamental cause may reside within processes of advantage and disadvantage that accumulate across the life course. Although education is a well-established risk factor for AD, it is unclear if the mechanistic role of education in AD disparities is through direct cognitive stimulation – the most commonly accepted hypothesis in AD research – or if it operates indirectly as a marker of social status and discrimination. **OBJECTIVES**: This dissertation aims to answer the question of how social processes at different points in the life course produce socioeconomic and racial inequalities in Alzheimer's disease risk. This question is broken into a series of three studies that examine the existing evidence for the role of modifiable risk factors in AD, and test for the role of cumulative advantage/disadvantage in the context of socioeconomic, and racial disparities. **METHODS**: Study one is a structured narrative review that evaluated studies that tested for differences by race of the effect of any of six modifiable risk factors (education, obesity, smoking, physical activity, social isolation, and psychosocial stress) for AD risk. Study two used a Generalized Estimating Equation to examine the effect of individual SES and state-level income inequality on Subjective Cognitive Decline, as reported in the Cognitive Decline module of the Behavioral Risk Factor Surveillance System. Study three used structural equation modeling to conduct mediation and conditional process analysis (moderated mediation) to examine the role of markers of socioeconomic status and stress in racial disparities in AD risk among participants of the National Social Life Health and Aging Project. **RESULTS**: Of 3,464 identified studies in study one, 45 tested for differences in

the modifiable risk factors by race. Education was the most widely examined risk factor, and the only factor in the review with strong evidence for a role in racial disparities. In study two, a dose-response effect was observed for income while those with high school education reported better cognition than those with some college. State-level income inequality was not associated with cognitive decline. In study three, education consistently mediated the race-cognition pathway, and perceived stress and assets mediated the education-cognition pathway. In all models, the direct effect of race on cognition remained large. **CONCLUSIONS**: Combined, these studies confirmed the importance of education for socioeconomic and racial disparities in AD risk, but suggested that education operates as an indicator of social status and discrimination, as well as through its role via cognitive stimulation. These findings point to the importance of considering social factors from across the life course in public health research and interventions aiming to understand and reduce disparities in AD risk.

CHAPTER 1: INTRODUCTION

Alzheimer's Disease Disparities and the Public Health Impact

The prevalence of Alzheimer's disease (AD) in the U.S. is projected to increase by about 45% over the next decade to 8.4 million cases (Alzheimer's Association, 2018). Although genetic risk and therapeutic intervention have been the primary focus of AD research over the past 30 years, the role of social epidemiology in this field is increasing amidst a growing recognition of the importance of risk reduction – achieved through intervening on modifiable risk factors (Livingston et al., 2017) – and the mounting evidence for socioeconomic and racial disparities in AD risk (Karlamangla et al., 2009; Koster et al., 2005; Mayeda, Glymour, Quesenberry, & Whitmer, 2016a; Mehta & Yeo, 2016; Sharp & Gatz, 2011; Yaffe et al., 2013).

The AD epidemic and associated disparities has broad implications for the public's health. AD is a progressive neurological disorder that, over time, decreases one's functional abilities. At the severe stage, individuals with AD require round-the-clock care and assistance with basic activities of daily living, including dressing, eating, bathing and toileting. As age is the leading risk factor for AD, the demographic shift toward an older society has already outpaced the capacity of available long-term care services, requiring families to provide an estimated 18.4 billion hours of unpaid care per year – a value of $232 billion (Alzheimer's Association, 2018). While acting as a family caregiver can be a meaningful experience, it often requires the caregiver to reduce their own paid employment – thereby also reducing their future retirement savings and employer-supplemented health insurance. Additionally, caregivers of persons with AD have worse mental and physical health – including higher rates of chronic disease – than non-caregivers (De Vugt & Verhey, 2013; Richardson, Lee, Berg-Weger, & Grossberg, 2013). As

such, disparities in AD may be both a marker and magnifier of processes of inequality, resulting in profound social and economic impacts across generations.

Etiology of Alzheimer's Disease

AD is broadly recognized as the product of both social and biological processes (McDonough & Allen, 2018). Although genetic risk matters, it is the interaction of genetic risk with modifiable factors that include social, behavioral and co-morbid conditions that produces AD (Karch & Goate, 2015; McDonough & Allen, 2018). Evidence suggests that the most impactful modifiable risk factors for Alzheimer's disease are education, mid-life hypertension, mid-life obesity, mid-life hearing loss, smoking, physical activity, depression, diabetes and social isolation (Livingston et al., 2017). The mechanisms that are hypothesized to connect these risk factors to AD are varied and not fully understood, though most – if not all – of the proposed "chains of risk" originate in social conditions, suggesting that social conditions are the "fundamental causes" of health disparities (Link & Phelan, 1995; Phelan, Link, & Tehranifar, 2010). For example, those with lower SES are less likely to engage in health promoting behaviors (Lawrence, 2017; Pampel, Krueger, & Denney, 2010), which increases the risk of chronic conditions such as hypertension, diabetes and other vascular risk factors that accelerate cognitive deficits (Cunningham & Hennessy, 2015; Kruyer, Soplop, Strickland, & Norris, 2015; Lu, Lin, & Kuo, 2009; Moonga, Niccolini, Wilson, Pagano, & Politis, 2017).

In the absence of a cure, addressing the modifiable risks of AD is the only effective approach to risk reduction. Despite the growing interest in the social determinants of AD, the underlying mechanisms of racial and SES disparities in AD are not yet clearly understood. Research pertaining to AD disparities is relatively new. Descriptive epidemiology studies show

consistent disparities between AA and NHW populations, while estimates for Latino and Asian populations vary – likely as a factor of national/ethnic origins – and there is insufficient data to estimate the prevalence of American Indian, Alaska Native or Native Hawaiian populations (Garcia et al., 2017; Masel & Peek, 2009; Mayeda, Glymour, Quesenberry, & Whitmer, 2016b; Mehta & Yeo, 2016). Similarly, studies on SES disparities vary, and education is the only factor with a consistent negative association with AD risk (Karlamangla et al., 2009; Koster et al., 2005; Sharp & Gatz, 2011). Studies from the fields of psychology and neurology have added critical knowledge regarding the potential for biased cognitive testing (Manly, Jacobs, Touradji, Small, & Stern, 2002) and the role of genetic and biological risk factors to explain these disparities (Hendrie, 2001). However, few studies have examined AD disparities in the context of the dominant theoretical frameworks used to explain social determinants of health in the *Sociology and Public Health literature* to advance understanding of the mechanisms underlying disparities in AD.

Theoretical Background

Social Determinants of Health and Cumulative Advantage/Disadvantage

Social determinants of health are broadly understood to be the product of the "inequitable distribution of power, money, and resources" that shapes daily living conditions and produces disparate health outcomes (World Health Organization Commission on Social Determinants of Health, 2008). One of the prevailing theoretical frameworks for conceptualizing social determinants of health is the social ecological model (Sallis, Owen, & Fisher, 2008). This model, which stems from systems theory, demonstrates that health is inherently the product of ongoing interactions between individuals and their interpersonal and structural environments

(Bronfenbrenner, 1975). However, the application of this model has shifted over time to bring more focus to individual agency (Tudge, Mokrova, Hatfield, & Karnik, 2009). This approach has resulted in a decontextualized emphasis on individual behavior as the dominant force for health outcomes. Applying the broader social and economic theory of Cumulative Advantage/Disadvantage (CAD) to studies that examine the social determinants of health and health disparities provides an important corrective (Dannefer, 2018; Myrdal, 1944; O'Rand, 1996).

The foundational premise of CAD is that social structure interacts with life course processes to produce inequalities that widen over time (Dannefer, 2018; DiPrete & Eirich, 2006). That social structure provides the geneses of disparities is the critical point. While this premise does not negate the possibility of individual resilience and agency in overcoming systemic disadvantages, it mandates researchers and interventionists alike to explicitly consider the role of social forces in health outcomes across the life course, rather than individual differences in biology, temperament or behavior (Dannefer, 2018; Pavalko & Caputo, 2013). This theoretical orientation therefore shapes the overarching question of this study: *How do social processes at different points in the life course produce socioeconomic and racial inequalities in Alzheimer's disease risk?*

While socioeconomic status and race are highly correlated, they are not equivalent. Racial disparities persist at every level of SES, demonstrating the cumulative nature of these statuses on health (Geronimus, 1992). As such, it is critical that potential mechanisms underlying race and SES disparities be examined separately (Kawachi, Daniels, & Robinson, 2005).

Social status, socioeconomic inequality and health disparities

It has long been common knowledge that living in poverty with severe material deprivation for food, clothing, housing and sanitation leads to poorer health (Braveman, Egerter, & Williams, 2011). However, evidence for the broader impact of social status on health emerged with Marmot's landmark Whitehall Studies of British Civil Servants, which documented a dose-response relationship between social status and health and shifted the focus from material deprivation to a broader recognition of social psychological factors in health (Marmot & Shipley, 1996; Marmot et al., 1991; Smith, Shipley, & Rose, 1990). This "social gradient in health" is theorized to operate via a stress response to social comparisons and hierarchical systems (Mullahy, Robert, Wolfe, Robert, & Wolfe, 2011).

An important element of the Durkheimian roots of Cumulative Advantage/Disadvantage (CAD) is that social stratification is a "social fact" (Durkheim, 1966). The allocation of resources in a society that contribute to CAD processes are not due to national selection, but are a product of social structure (Dannefer, 2018; Durkheim, 1966). A pertinent example of how stratification is inherent to social systems is the career classification system, such as that studied by Marmot, where each successive level has fewer opportunities for advancement due to the pyramid structure of most organizations. This is not to say that individual differences do not exist, but merely to recognize that social stratification does not emerge in reflection of these differences. Rather, the resources one is born with (or without) set the foundation for accumulation of advantage or disadvantage across the life course, with substantial impacts for health (Pavalko & Caputo, 2013).

CAD is a driving force for population level inequality (DiPrete & Eirich, 2006), and inequality shapes the intraindividual social gradients such that gradients in less equal societies will have steeper slopes (Pickett & Wilkinson, 2015). These wider differences are theorized to produce a stronger sense of "status anxiety" and heightened levels of psychosocial stress than those societies with a flatter social gradient (Pickett & Wilkinson, 2015; Wilkinson & Pickett, 2017). Inequality may also contribute to disparate health outcomes through lower levels of public support and funding for education, social services and health care that have been observed in less economically equal societies (Bradley et al., 2016; Kawachi & Kennedy, 1999).

Race and health disparities

A second body of literature has emerged in parallel to the "status anxiety" perspective to explore how racialized experiences produce disparate health outcomes above and beyond those accounted for by SES. The dominant theory for this work is the "weathering hypothesis," which emerged in an effort to explain why AA women who are college educated have birth outcomes comparable to NHW women with high school educations (Geronimus, 1992). This theory suggests that ongoing exposure to discrimination activates the body's stress response system and accelerates the aging process, (Geronimus, Hicken, Keene, & Bound, 2006). This theory embodies one of the core tenets of CAD, that exposures across the life course – including in late life – are pertinent to understanding disparities (Dannefer, 2018).

Cumulative Advantage/Disadvantage Theory and Alzheimer's disease

Cognitive reserve

Systematic reviews and meta-analyses have observed a consistent relationship between education and age-related cognition, with some reporting a dose-response effect (Meng &

D'Arcy, 2012; Xu et al., 2016). This suggests that as more educated cohorts age, the prevalence of AD may drop (Leggett et al., 2019). However, educational attainment is also a prominently considered factor in health disparities.

In the broader health disparities literature, there are several mechanisms by which education influences health. At the individual level, education impacts health literacy and health behaviors (Lawrence, 2017; Mirowsky & Ross, 2005). At the structural level, education is a dominant component of SES, and serves to reinforce one's social status and provide access to health promoting resources and environments (Cockerham, 2005; Pavalko & Caputo, 2013; Phelan et al., 2010). This interpretation stands in contrast to the most frequently cited mechanism of the relationship between education and AD risk: cognitive reserve. The cognitive reserve hypothesis emerged to explain why individuals with similar levels of AD pathology have vastly different clinical symptoms (Meng & D'Arcy, 2012; Stern, 2009; Stern & Habeck, 2018). Cognitive reserve is not a measure of pathology, but rather "speaks to how well somebody utilizes their brain regardless of how well it has been preserved" (Stern & Habeck, 2018). This is a critical factor for onset of AD, as the disease is diagnosed clinically based on symptoms and a decline in cognitive capacities, rather than via tests that demonstrate the presence of pathology.

The exact mechanisms of cognitive reserve are not yet known. Currently, testing for cognitive reserve involves using a direct clinical measure of cognitive function, such as those that would be used in clinical settings to diagnose AD (e.g. mini-COG), biomarkers of AD neuropathology observed via neuroimaging, and a hypothesized *proxy* of cognitive reserve, which is frequently educational attainment, IQ or literacy (Stern & Habeck, 2018). This approach thereby assumes that education and other proxies of cognitive reserve are operating via a direct

effect of cognitive stimulation (Arenaza-Urquijo, Wirth, & Chételat, 2015; Chapko, McCormack, Black, Staff, & Murray, 2017; Opdebeeck, Martyr, & Clare, 2016). This assumption disregards the broader health disparities literature and the competing hypotheses of status anxiety and weathering, and may hinder comprehensive public health efforts for AD risk reduction by narrowly focusing on targeting individuals with "brain training" to increase cognitive stimulation (Leshner, Landis, Stroud, & Downey, 2017; Shah, Weinborn, Verdile, Sohrabi, & Martins, 2017).

Allostatic load

Chronic stress is recognized by both the weathering hypothesis and status anxiety theory as the key biological pathway for social stratification and inequality to get "under the skin" and influence physical and cognitive health (Geronimus et al., 2006; Green & Darity, 2010; Juster, McEwen, & Lupien, 2010; McEwen, 2012; Mishra & Carleton, 2015; Singh-Manoux, Adler, & Marmot, 2003). The biological response to stress is the activation of the hypothalamic pituitary adrenal axis and the sympathetic adrenal medullary axis (Sapolsky, Romero, & Munck, 2000). Acute activation of these systems increases stress hormones such as epinephrine, norepinephrine and cortisol, and activates immune response through release of cytokines to prepare the body for "fight or flight." Chronic activation of this response contributes to a dysregulation of the metabolic, cardiovascular and immune systems, contributing to chronic disease risk and accelerated biological aging (McEwen, 2003). This overactivation is measured via a composite of biomarkers referred to as allostatic load (Juster, McEwen, & Lupien, 2010; McEwen & Seeman, 1999).

Organization of Dissertation

This series of studies seeks to answer the question of how social and structural processes at different points in the life course produce socioeconomic and racial inequalities in Alzheimer's disease risk. Chapter Two provides a starting point for this investigation through a review of the evidence for six modifiable risk factors in explaining racial disparities in AD risk. To date, reviews and reports that have identified the importance of modifiable risk factors have failed to consider if difference in prevalence of these factors or a differential strength of effect by race will help to explain racial disparities in AD (Livingston et al., 2017). Using a structured search process, I addressed this question by synthesizing the evidence from identified studies that explicitly tested for and reported findings for differences by race in six modifiable risk factors (smoking, obesity, education, psychosocial stress, social isolation and physical activity).

Chapters three and four utilize national data sets that have pertinent cognitive and social measures for mid-life and older adult participants that allow for the social epidemiological study of CAD processes on Alzheimer's disease risk. In Chapter three I focus on the role of SES and income inequality in AD risk using the Behavioral Risk Factor Surveillance System, an annual telephone survey of self-reported health and behaviors conducted by the U.S. Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2014). The system interviews more than 400,000 community-dwelling adults from across all 50 states and Washington D.C., and is the largest health survey system in the world (Centers for Disease Control and Prevention, 2014). In the study, I test for the presence of a social gradient in cognitive decline and for a contextual effect of state-level income inequality on cognitive decline after controlling for individual SES. The explicit test for social context in individual risk in this

study appropriately acknowledges the structural forces that contribute to CAD and influence disparate health outcomes.

Chapter four provides a test of the cognitive reserve hypothesis and weathering hypotheses as explanatory factors for racial disparities in Alzheimer's disease risk. For this study, I utilize the restricted version of the National Social Life Health and Aging Project (NSHAP) dataset, conducted by the National Opinion Research Center at the University of Chicago (Waite, 2017; Waite, Cagney, et al., 2014; Waite, Laumann, Levinson, Tessler Lindau, & O'Muircheartaigh, 2014). The dataset is a cohort study currently consisting of three waves of data collected every three years, starting in 2005, and includes cognitive tests and measures of stress, including appropriate biomarkers for measuring allostatic load (Shega et al., 2014; Shiovitz-Ezra, Leitsch, Graber, & Karraker, 2009; Waite, Laumann, et al., 2014). This study uses mediation analyses to examine if the effect of education on cognitive function is mediated by other markers of social status (measured via income or accumulated wealth), by status anxiety (measured by subjective social status) or by weathering (measured with allostatic load and perceived stress). This approach considers the contributions of factors from across the life course (educational attainment, accumulated wealth), and the interactive response between individuals and structural systems to produce psychological (perceived stress; subjective social status) and biological (allostatic load) effects that may contribute to AD disparities.

Chapter Five summarizes the findings from Chapters Two, Three and Four, and provides recommendations for furthering this line of inquiry and continuing to advance the science for understanding and intervening on AD risk.

CHAPTER 2: THE ROLE OF SOCIAL AND BEHAVIORAL RISK FACTORS IN EXPLAINING RACIAL DISPARITIES IN AGE-RELATED COGNITIVE IMPAIRMENT: A STRUCTURED NARRATIVE REVIEW

Background

Significant racial disparities have been observed in Alzheimer's disease and related dementias. A recent review of prevalence and incidence studies across racial/ethnic populations found that African Americans (AAs) have consistently higher rates of Alzheimer's disease and related dementias when compared with non-Hispanic Whites (NHWs), though the degree of disparity varies across studies (Mehta & Yeo, 2016). Alzheimer's disease, the most common form of dementia, results in declines in cognitive and physical functioning that, over time, increase the need for personal care in activities of daily living. With inadequate availability of long-term care services, many families of individuals living with dementia reduce their paid employment to take on roles of caregiving, with broader consequences for their own health (Alzheimer's Association, 2018; Richardson et al., 2013). As the number of individuals diagnosed with Alzheimer's disease continues to increase, so will its impacts to families and society, and the disparities between AAs and NHWs may widen if the risks driving them are not better understood and effectively addressed (Hebert, Weuve, Scherr, & Evans, 2013).

Racial disparities have been observed across a wide array of health conditions, with a complex network of factors likely contributing. The National Institutes on Aging Health Disparities Research Framework points to factors across environmental, sociocultural, behavioral and biological levels of analysis that should be explored to understand health disparities (C. V. Hill, Pérez-Stable, Anderson, & Bernard, 2015). While biological factors, such as genetic risk,

set the stage for Alzheimer's disease risk, it is the exposure and accumulation of environmental, sociocultural and/or behavioral factors that shapes the vulnerability to biological risk and likely produces the disparate rates of Alzheimer's disease among AAs (McDonough & Allen, 2018). It is therefore critical to distinguish between biological *differences* in risk and the embodiment of social discrimination that drives racial health *disparities* (Gravlee, 2009; Krieger, 2000a). In other words, racial disparities in Alzheimer's disease are not biological, but a function of modifiable environmental, sociocultural and behavioral mechanisms that shape AD risk and are therefore modifiable.

The Lancet Commission on Dementia Prevention, Intervention and Care has identified nine modifiable risk factors that account for 35% of population attributable risk of dementia: education, mid-life hypertension, mid-life obesity, mid-life hearing loss, smoking, physical activity, depression, diabetes and social isolation (Livingston et al., 2017). However, much of what is known about Alzheimer's disease risk is rooted in research that tends to underrepresent AAs and other minorities, limiting knowledge of how known risk factors across racially and ethnically diverse populations may be distributed and if they operate similarly across groups. Such gaps have been identified for biological risks of Alzheimer's disease, and may similarly be a major concern for understanding the potentially modifiable environmental, sociocultural and behavioral risks that influence AD disparities (Haga, 2010). Indeed, the Lancet review focused on studies largely published on populations in Europe and the United States, and did not explore possible racial variation in risk (Livingston et al., 2017). Of the risks identified in the Lancet report, AAs have higher prevalence rates of some factors, though not all (Keadle, McKinnon, Graubard, & Troiano, 2016; Menke, Casagrande, Geiss, & Cowie, 2015; Nwankwo, Yoon, Burt,

& Gu, 2013; United States Census Bureau, 2016). As there is currently no effective treatment for Alzheimer's disease, our best approach for reducing racial disparities is in understanding if and how the relationship between modifiable risks and Alzheimer's disease varies by race and developing interventions to target these factors.

The aim of this review is to compile and evaluate if the evidence for known social and behavioral modifiable risk factors for Alzheimer's disease helps to explain the observed disparities between AAs and NHWs. While the Lancet report identified nine modifiable risk factors, we chose to focus this review on five: education, smoking, physical inactivity, social isolation and obesity. We selected these as priority modifiable risk factors for racial disparities because they are 1.) most likely to precede others in a chain of risk (e.g. low education is associated with physical inactivity, which can contribute to obesity, which is a risk for hypertension, which is a risk for Alzheimer's disease); and 2.) are plausibly responsive to intervention (including policy change) and therefore amenable to risk reduction in Alzheimer's disease. Although not highlighted by the Lancet review, we also included psychosocial stress as a social risk for Alzheimer's disease in the review, given the growing evidence it is a key mechanism for the social environment to "get under the skin" and drive health disparities in a broad range of health outcomes (Geronimus, 1992; Geronimus et al., 2006; McEwen, 2012). Our findings are expected to provide direction for intervention and risk reduction of Alzheimer's disease in African American populations and identify gaps for future research.

Methods

We conducted a structured narrative review that combined a systematic, documented search strategy with supplemental searches and citation review to ensure our search was both

comprehensive and targeted to our research aim. While systematic reviews are considered the gold standard for synthesizing the state of evidence in areas where there is a rich source of empirical studies and where elements of study design strength can be assessed, we determined that a narrative review more appropriately fits the goal of this project (Higgins & Green, 2011). Consequently, our approach allowed us to include studies of diverse methods and aims that provided pertinent evidence for our research aim. At the same time, we sought to overcome a subjectivity bias in the selection of included articles through the systematic structured search component, and to provide documentation that would allow for replication, addressing two common critiques of narrative reviews (Ferrari, 2015).

Search Strategy

We used a three-step search strategy that included a systematic literature search, exploratory searches, and citation review. The systematic search was conducted in June 2018. We searched Pubmed, Embase, Psychinfo and Sociological Abstracts using MeSH (or equivalent) terms for peer-reviewed, English language papers. We conducted additional expansive keyword searches for each of the risk factors in the aforementioned databases from June 2018 to July 2018. Finally, we reviewed the citations of the included studies for additions that met our inclusion/exclusion criteria. Table 1 provides an example of a complete search strategy in PubMed for one risk factor. Comparable searches were completed for each of the risk factors in all four databases.

Inclusion and Exclusion Criteria

We used a standardized rubric with pre-specified criteria to identify studies for inclusion (see Appendix A). A study was included if it: 1) analyzed as a primary outcome cognitive

function at a single point in time, rate of cognitive change over time, and/or Alzheimer's disease incidence. Although our primary interest is in explaining racial differences in Alzheimer's disease, we found it important to include studies that looked at both cross-sectional cognitive function and rate of cognitive decline over time, as these studies provide larger population

TABLE 1. *Example of the three-step search strategy in the PubMed database.*

Search Strategy	Search Terms	Yield	Included
Structured search (PubMed search - all risk factors)	(("African Americans"[Mesh]) AND (("Cognitive Dysfunction"[Mesh]) OR "Alzheimer Disease"[Mesh])) AND ((((((("Obesity"[Mesh]) OR "Stress, Psychological"[Mesh]) OR "Smoking"[Mesh]) OR "Social Isolation"[Mesh]) OR "Educational Status"[Mesh]) OR "Exercise"[Mesh])	37	1
Supplemental Search (PubMed - obesity only)	(((((("African Americans"[Mesh] OR black)) OR biracial)) AND ((((Alzheimer's disease) OR cognitive impair*) OR cognitive decline) OR memory loss)) AND ((((BMI) OR Body Mass Index) OR Overweight) OR Obesity)	83	5
Citation Review (obesity only)	Reviewed all included studies identified from structured and supplemental searches for all risk factors.	NA	0

estimates that are indicative of Alzheimer's disease risk before the onset of disease. While not all individuals who have a low cognitive function score or cognitive decline will progress to Alzheimer's disease, inclusion of these studies substantially increases the studies that meet inclusion criteria and helps to minimize bias from looking only at those populations who have been willing and able to seek medical services that resulted in an Alzheimer's disease diagnosis.

We also focused exclusively on studies that 2) quantitatively tested for differences in AAs and NHWs 3) in the effect of one or more of the six social and behavioral modifiable risk factors that are the focus of this review, and were 4) cohort or cross-sectional observational studies of 5) community-dwelling mid-life and older adults who did not have another health issue that might impact their cognition (e.g. history of lupus). We did not specifically set age parameters on included studies, though because of the focus on Alzheimer's disease almost all study participants were ages 45 and older. However, we recognize that many individuals living

with Alzheimer's disease have mixed dementia that includes vascular dementia, which is strongly associated with a history of stroke (Schneider, Arvanitakis, Bang, & Bennett, 2007).

Analysis

For each included study, we compiled findings on the associations between the risk factor and cognitive outcomes (cognitive function as a single time point, rate of cognitive decline and incidence Alzheimer's disease), and if these relationships varied by race. We summarized this evidence by risk factor and classified our findings as strong, moderate or weak/inconclusive for explaining racial disparities in Alzheimer's disease risk. We considered the evidence to be strong if the findings for the relationship between the risk factor and race for each of the cognitive outcomes were consistent across studies, moderate if findings across studies were consistent for at least one of the cognitive outcomes but inconsistent or unavailable for the other cognitive outcomes, and weak/inconclusive if findings were inconsistent across one or more of the cognitive outcomes.

Results

Included Studies

The structured searches yielded 3,298 non-duplicated articles. Of these, 36 were included in full text review, and 18 met our criteria for inclusion in our analysis. Through keyword supplemental searches, we identified an additional 23 studies that met our criteria and through citation review we identified an additional 4 studies. Figure 1 provides the CONSORT flow diagram for our search and limitation process. Table 2 provides the complete list of included studies and the evaluated risk factors for each.

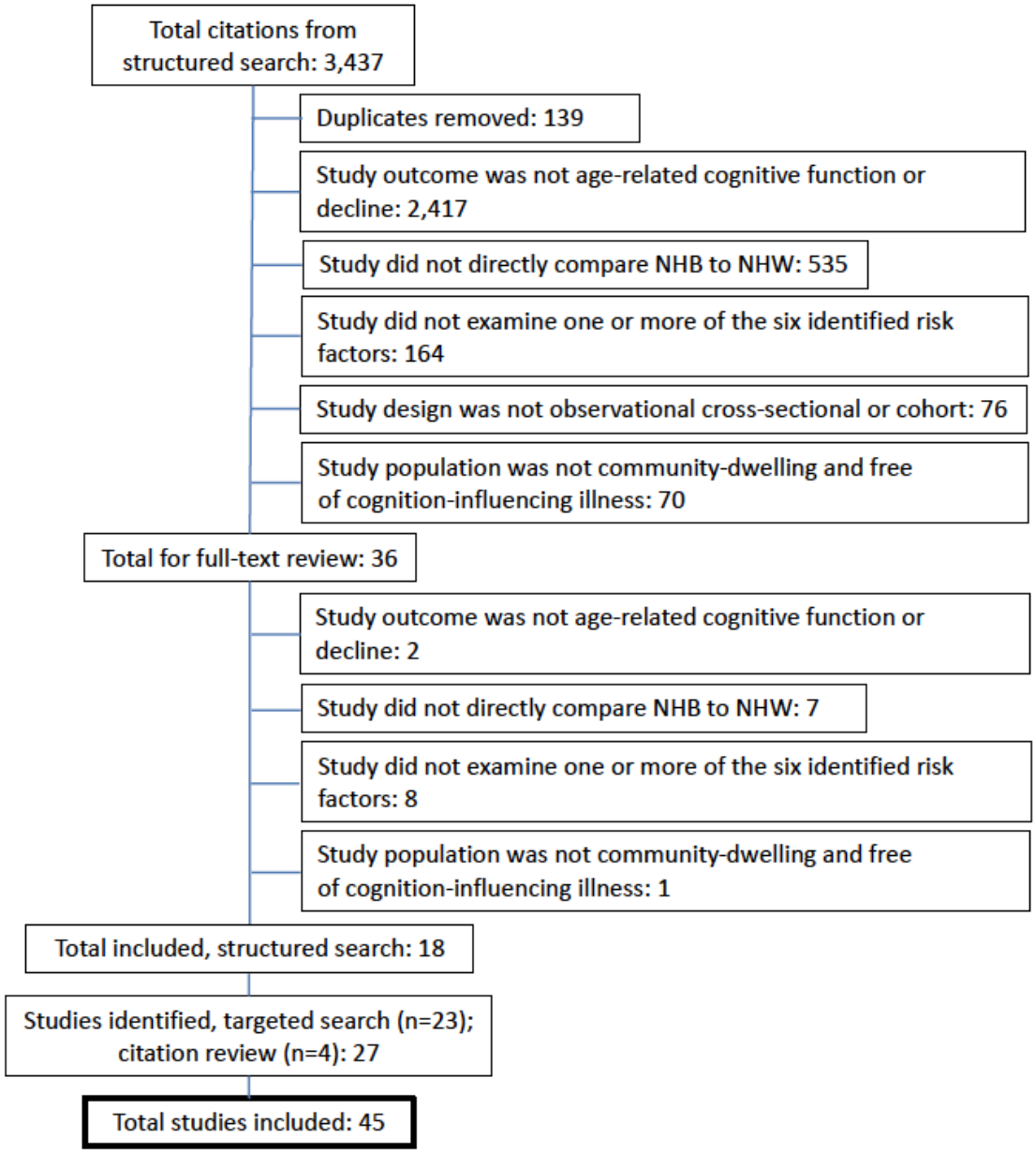

FIGURE 1. *Flow diagram of included studies.*

TABLE 2. *List of included studies by risk factor(s) and cognitive outcome(s).*

Citation	Participants	Data Source	Outcome(s)	Risk factor(s)
Arpawong, et. al., 2016	AA (n=1,558); NHW (n=9,351); Hispanic (n=1,079)	Health and Retirement Study	Cognitive decline	Education
Barnes, et. al., 2005	AA (n=125); non-AA (n=327)	Patients of Rush Alzheimer's Disease Center, and Chicago-area adult day centers	Cognitive decline	Education
Barnes, et. al., 2011	AA (n=6,083); NHW (n=3,541)	Chicago Health and Aging Project	Cognitive function	Education
Garcia, et. al. 2018	AA (n=3,715); NHW (n=12,762) US-born Hisp. (n=992); Foreign-born Hisp. (n=1,630)	Health and Retirement Study	Cognitive Impairment and Dementia incidence	Education
Wilson, et. al. 2009	AA (n=4377); NHW (n=2156)	Chicago Health and Aging Project	Cognitive decline	Education
Rodriguez et. al., 2018	**Low education:** AA (n=121); NHW (n=215); Hispanic (n=71) **High education:** NHW (n=375); non-NHW (n=37)	ADAMS HRS	Dementia incidence	Education
Crowe, et. al., 2013	AA (n=223) NHW (n=210)	University of Alabama-Birmingham Study of Aging	Cognitive function and decline	Education Quality
Liu, et. al., 2015	**HRS:** AA (n=2,362) NHW (n=13,313) **WHICAP:** AA (n=1,013) NHW (n=540)	Health and Retirement Study; Washington Heights-Inwood Columbia Aging Project	Cognitive function	Education Quality
Sisco, et. al., 2015	Black (n=1,192) White (n=487) Note: Hispanic included in above categories	Washington Heights-Inwood Columbia Aging Project	Cognitive function	Education Quality

Reuser, et. al., 2011	AA (n=3,294) NHW (n=17,342) Hispanic (n=762)	RAND Health and Retirment Study	Cognitive function	Education Obesity Smoking
Masel, et. al. 2010	AA (n=1,612) NHW (n=6,723) Hispanic (n=869)	Health and Retirement Study	Cognitive function	Education Physical Activity
Vasquez, et. al. 2015	AA (n=548) NHW (n=2,652) Hispanic (n=224)	Health and Retirement Study	Cognitive function and decline	Education Physical Activity Smoking
Carvalho, et. al. 2015	AA (n=118); NHW (n=461)	Memory Health and Aging study	Cognitive function and decline	Education/Literacy
Chin, et. al., 2012	AA (n=51) NHW (n=193)	University of Pennsylvania Alzheimer's Disease Center patients	Cognitive function	Education/Literacy
Crowe, et. al., 2008	AA (n=299); NHW (n=311)	University of Alabama-Birmingham Study of Aging	Cognitive function	Education/Literacy
Dotson, et. al., 2009	AA (n=757); NHW (n=588)	Healthy Aging in Neighborhoods of Diversity across the Life Span	Cognitive function	Education/Literacy
Kaup, et. al. 2014	AA (n=932);NHW (n=1526)	Health Aging and Body Composition	Dementia incidence	Education/Literacy
Manly, et. al., 2002	AA (n=192); NHW (n=192)	Washington Heights-Inwood Community Aging Project	Cognitive function	Education/Literacy
Sachs-Ericsson, et. al., 2005	AA (n=1,690); NHW (n=1,407)	Duke Established Populations for Epidemiologic Studies of the Elderly	Cognitive decline	Education/Literacy
Yaffe, et. al., 2009	AA (n=897) NHW (n=1612)	Health Aging and Body Composition Study	Cognitive resilience (absence of cognitive decline)	Education/Literacy Isolation Obesity Physical Activity Smoking
Kaup, et. al. 2015	AA (n=329) NHW (n=341)	Health Aging and Body Composition Study	Cognitive resilience (absence of cognitive decline)	Education/Literacy Isolation Obesity Physical Activity Smoking

Kuczmarski, et. al., 2015	AA (n=972) NHW (n=772)	Healthy Aging in Neighborhoods of Diversity across the Life Span	Cognitive function	Education/Literacy Obesity
Barnes, et. al., 2004	AA (n=2,421); NHW (n=1,478)	Chicago Health and Aging Project	Cognitive decline	Isolation
Han, et. al. 2016	AA (n=590); NHW (n=590)	Rush Memory & Aging Project; Minority Aging Research Study	Cognitive function	Isolation
Kats, et. al., 2016	AA (n=3,090); NHW (n=10,029)	Atherosclerosis Risk in Communities Study	Cognitive function and decline	Isolation
Zahodne, et. al., 2017	AA (n=225); NHW (n=170); Hispanic (n=153)	Washington Heights-Inwood Columbia Aging Project	Cognitive function	Isolation
Arvanitakis, et. al., 2018	AA (n=704); NHW (n=1,430)	Minority Aging Research Study; Rush Memory and Aging Project	Cognitive decline	Obesity
Bressler, et. al., 2013	AA (n=2,083); NHW (n=8,364)	Atherosclerosis Risk in Communities Study	Cognitive decline	Obesity
Bryant, et. al., 2014	AA (n=546) NHW(n=4,104 Hispanic (n=110)	Health and Retirement Study (2010)	Cognitive function	Obesity
Gottesman, et. al., 2017	AA (n=4,267) NHW (n=11,477)	Atherosclerosis Risk in Communities Study	Dementia incidence	Obesity
Hu, et. al., 2012	AA (n=25,042) NHW (n=19,618)	Louisiana State University hospital-based longitudinal study	Dementia incidence	Obesity
Rajan, et. al., 2014	AA (n=2,834) NHW (n=1,221)	Chicago Health and Aging Project	Cognitive function and decline	Obesity
Sturman, et. al., 2008	AA (n=2,371) non-AA (n=1,514)	Chicago Health and Aging Project	Cognitive function and decline	Obesity
Rajan, et. al. 2015	AA (n=4,976); NHW (n=2766)	Chicago Health and Aging Project	Cognitive decline	Physical Activity

Zhu, et. al. 2017	AA (n=1,968);NHW (n=4,484)	Reasons for Geographic and Racial Differences in Stroke project	Cognitive decline	Physical Activity
Zhu, et. al. 2015	AA (n=2,234); NHW (n=4,864)	Reasons for Geographic and Racial Differences in Stroke project	Cognitive function	Physical Activity
Aggarwal, et. al., 2014	AA (n=4,081) NHW (n =2,126)	Chicago Health and Aging Project	Cognitive function and decline	Psychosocial Stress
Kaup, et. al. 2015	AA (n=329) NHW (n=341)	Health Aging and Body Composition	Cognitive resilience (absence of cognitive decline)	Psychosocial Stress
Sheffler, et. al. 2014	AA (n=2,235) NHW (n=1,877)	Duke Established Populations for Epidemiologic Studies of the Elderly	Cognitive function	Psychosocial Stress
Wilson, et. al., 2005	AA (n=570) NHW (n=575)	Chicago area residents age 65 and older.	Alzheimer's disease incidence	Psychosocial Stress
Wilson, et. al., 2005b	AA (n=2,723) NHW (n=1,669)	Chicago Health and Aging Project	Cognitive function and decline	Psychosocial Stress
Zuelsdorff, et. al., 2017	AA (n=82) NHW (n=1,232)	Wisconsin Registry for Alzheimer's disease Prevention (WRAP)	Cognitive function	Psychosocial Stress
Aggarwal, et. al., 2006	AA (n=530) Non-AA (n=534)	Chicago Health and Aging Project	Alzheimer's disease incidence	Smoking
Bachman, et. al., 2003	AA (cases=285; controls=158) NHW (cases=1,650; controls=686)	Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study	Alzheimer's disease incidence	Smoking
Knopeman, et. al., 2001	AA (n=3,455) NHW (n=10,593)	Atherosclerosis Risk in Communities Study	Cognitive function	Smoking

Cognitive Function, Cognitive Decline and Alzheimer's Disease Incidence

Of the included studies, 30 examined effects on cognitive function at a single point in time, 26 examined effects on cognitive decline over time, and six examined effects on incident Alzheimer's disease or non-differentiated dementia. Ten out of 30 studies that included cognitive function as an outcome reported racial comparisons of baseline cognitive function unadjusted for the risk factor(s) of interest (Barnes et al., 2011, 2005; Carvalho et al., 2015; Crowe, Clay, Sawyer, Crowther, & Allman, 2008; Kuczmarski, Cotugna, Mason, Evans, & Zonderman, 2015; Liu, Glymour, Zahodne, Weiss, & Manly, 2015; Masel, Raji, & Peek, 2010; Sachs-Ericsson & Blazer, 2005; Sheffler, Moxley, & Sachs-Ericsson, 2014; Vásquez, Botoseneanu, Bennett, & Shaw, 2015). Of these, all observed that AAs had lower cognitive function for most or all of the domains examined. Two of the six studies with incident dementia as an outcome reported unadjusted dementia incidence by race. One found that AAs had a higher risk of dementia (Garcia, Saenz, Downer, & Wong, 2018), while the second found that unadjusted risk was equal for NHWs and AAs (Rodriguez, Aranda, Lloyd, & Vega, 2018). No studies reported unadjusted comparisons of cognitive decline by race.

Study cohorts and geographic dispersion

Twenty cohorts or locally-recruited populations were analyzed in the 45 included studies. The most frequently used cohorts were the Chicago Health and Retirement Project (n=9) and the nationally representative Health and Retirement Study (n=7). Most of the research studies included in this analysis relied on populations residing in the Northeast or Southeast regions of the United States. This pattern is logical as these regions tend to have higher densities of AAs than other parts of the U.S., though it limits the generalizability of findings. Table 3 provides a

complete list of geographic research sites and number of studies published for each site by risk factor.

We report the remainder of our findings by risk factor from those with the most to least identified studies. Studies that examined more than one of the risk factors of interest are discussed in all relevant sections. We also discuss patterns in findings in each section separately for each of the three cognitive outcomes. Table 4 provides a summary of our findings.

TABLE 3. *Geographic locations of included studies by risk factor.*

City/ Region of Study	Years of Ed.	Ed. & Literacy	Qual. of Ed.	Obesity	Physical Activity	Psycho-social Stress	Smoking	Social Isolation
National	**6**		**1**	**2**	**2**		**3**	
Northeast	**0**	**7**	**2**	**4**	**2**	**1**	**4**	**4**
NY, NY		1	2					1
Baltimore, MD		2		2			2	1
Phila., PA		1						
Pittsburg, PA		3		2	2	1	2	2
Southeast	**0**	**6**	**1**	**7**	**4**	**1**	**4**	**4**
Alabama		1	1		2			
Louisiana				1				
Jackson, MS				2			1	1
North Carolina		2		2			1	1
Memphis, TN		3		2	2	1	2	2
Midwest	**3**	**0**	**0**	**5**	**1**	**4**	**2**	**3**
Chic., IL	3			3	1	3	1	2
Minn., MN				2			1	1
Wisconsin						1		

TABLE 4. *Summary of the evidence and research gaps for each risk factor.*

Risk factor	Outcome of Interest	State of Evidence	Research Gaps
Social Isolation (n=6)	Cognitive function (n=3)	Isolation is associated with cognitive function, but there is no difference by race. It is inconclusive if social isolation is more prevalent in one race group.	Future research should examine prevalence in social isolation by race among older adults and explore if different measures of social isolation produce more consistent findings. Studies and data sets that connect social measures, including isolation, to incident AD are needed.
	Cognitive decline (n=4)	Studies contradict if social support is more protective for NHW, or if there is no effect for either race group.	
	Incident AD or other dementia (n=0)	NA	
Psychosocial Stress (n=6)	Cognitive function (n=2)	Studies contradict if the negative effect of stress is stronger for AAs or NHWs. Moderate evidence suggests stress is more likely among AAs.	Studies relied on self-report measures of stress or stressful life events. Future studies should also examine the role of stress biomarkers. The finding for AD incidence is based on one study; future studies are needed to substantiate this evidence.
	Cognitive decline (n=4)	Stress is associated with faster cognitive decline. Studies contradict if this effect is stronger in NHWs or AAs, or there is no difference by race.	
	Incident AD or other dementia (n=1)	Stress is predictive of AD in NHWs but not AAs.	
Obesity (n=10)	Cognitive function (n=4)	Studies contradict if obesity is positively or negatively associated with cognitive function for AAs while having no effect in NHWs, or if there is no effect for either race.	The relationship between BMI and cognitive function is complex and follows a u-shaped curve. High mid-life BMI is a vascular risk factor while low and declining late-life BMI is an indicator

	Cognitive decline (n=4)	Findings contradict if there is an effect, and if the effect varies by race.	of AD. Mean follow up times between BMI and cognitive testing in the included studies ranged from 0 to 23 years. Future research should aim to disentangle how the timing of obesity impacts AD risk.
	Incident AD or other dementia (n=2)	Studies contradict if obesity is a risk or protective factor for AD, and if this varies by race.	
Physical Activity (n=7)	Cognitive function (n=3)	Evidence suggests that physical activity is protective. The protective effect may be stronger for AAs, and partially attenuate racial disparities.	Because effects were predominately observed for cognitive function, future research should explore the association between physical activity throughout middle and late adulthood and incident AD.
	Cognitive decline (n=3)	Studies are contradicted on if physical activity is protective for only NHWs, for both race groups, or has no effect in either race group.	
	Incident AD or other dementia (n=0)	NA	
Smoking (n=8)	Cognitive function (n=5)	Studies are contradicted on if smoking has an effect. Those showing an effect did not observe a difference by race. One study found smoking may partially attenuate racial disparities.	Future research should look at possible third causes that would better connect smoking with racial disparities in AD. Reference group varied by study.
	Cognitive decline (n=4)	Studies are contradicted on if smoking has an effect. None observed a difference by race.	
	Incident AD or other dementia (n=0)	NA	

Years of Education (n=9)	Cognitive function (n=4)	Evidence suggests that years of education is protective and attenuates racial disparities. One study found a stronger protective effect for AAs versus NHWS with ≥12 years of education.	The key hypothesized biological mechanism for education is cognitive reserve: Education is also associated with health behaviors that lower vascular risks, including not smoking, healthy eating and more physical activity. Only three of the 22 studies included in this review examined incident AD, while 13 focused on cognitive function tests. Part of the educational effect observed may be therefore driven by testing bias. Future research should examine the effects on incident AD and explore the potential mediators of the education-AD relationship, including socioeconomic, behavioral and biological/cognitive reserve pathways.
	Cognitive decline (n=4)	Education is protective in both race groups. One study found a protective effect for APOE-e4 gene allele carriers only among NHW women .	
	Incident AD or other dementia (n=2)	Education is predictive of incident AD and may partially attenuate racial disparities.	
Literacy (n=10)	Cognitive function (n=6)	Literacy has an effect that may vary by socio-economic position for NHWs but not AAs. Literacy partially or fully attenuates racial disparities.	
	Cognitive decline (n=3)	Literacy is protective for both race groups and may attenuate racial disparities.	
	Incident AD or other dementia (n=1)	Literacy is predictive of incident AD in both races, though AAs have lower literacy levels.	
Quality of Education (n=3)	Cognitive function (n=3)	School quality is associated with cognitive function. The effect differs by race depending on the measure used and geographic location of the study.	
	Cognitive decline (n=0)	NA	

	Incident AD or other dementia (n=0)	NA	

Education

We identified 22 studies that examined education. Of these, nine focused on years of education, 10 examined years of education in conjunction with literacy level, and three examined quality of childhood education. We did not explicitly search for studies examining school quality or literacy level, but this sub-categorization emerged upon review. As such, we are reporting our findings based on these subcategories of education to allow for a more detailed interpretation of possible mechanisms underscoring any observed associations.

Years of Education. In bivariate analysis, four studies observed lower education levels among AAs (Barnes et al., 2005; Garcia et al., 2018; Masel et al., 2010; Wilson et al., 2009), and one observed no difference by race (Vásquez et al., 2015). In adjusted analysis for the effect on cognitive function, two studies found that years of education partially attenuated racial disparities (Masel et al., 2010; Vásquez et al., 2015). One study observed that education was protective for both AAs and NHWs (Reuser, et. al., 2011), and another found that the protective effect of having more than 12 years of education was stronger in AAs than NHWs, while there was no racial difference in effect at less than 12 years (Barnes et al., 2011).

In examination of cognitive decline, two studies observed the effect of education was equivalently protective in both race groups (Barnes et al., 2005; Vásquez et al., 2015). One study identified a non-linear association where less education was protective against cognitive decline in earlier years, but more education was protective in later years, though this pattern did not vary

by race (Wilson et al., 2009). By contrast, another study found that while education was protective in both race groups for those without the genetic risk factor APOE ε4, education is only protective for NHW women with APOE ε4 (Arpawong, McArdle, & Prescott, 2016). Among the two studies that examined the effect on incident dementia, one found that education attenuated racial disparities (Garcia et al., 2018), while another found that there was no difference by race in incident dementia among those with lower educational attainment (Rodriguez et al., 2018).

These findings suggest that educational attainment is associated with Alzheimer's disease in both races, and that the lower educational attainment among the AA population may be an important contributor to racial disparities in Alzheimer's disease.

Literacy. In studies that reported bivariate associations by race, all found that AAs had significantly lower literacy levels than NHWs (Carvalho et al., 2015; Chin, Negash, Xie, Arnold, & Hamilton, 2012; Kaup et al., 2014; Kuczmarski et al., 2015; Manly et al., 2002; Sachs-Ericsson & Blazer, 2005). In adjusted analysis of cognitive function, one study observed an association with education and literacy in both races (Kuczmarski et al., 2015). Another study found that literacy level was associated with cognitive function in all AAs, but only NHWs with low socioeconomic status (Dotson, Kitner-Triolo, Evans, & Zonderman, 2009). Four studies examined literacy and education as mediators for the relationship between race and cognitive function, and found that education and literacy combined partially (Manly et al., 2002) or fully (Carvalho et al., 2015; Chin et al., 2012; Crowe et al., 2008) attenuated racial differences in cognitive function.

For rate of cognitive decline, two studies observed that the effect of literacy was protective for both NHWs and AAs ((Kaup et al., 2015; Yaffe et al., 2009), while one study found that the relationship between race and rate of decline was mediated by education and literacy (Sachs-Ericsson & Blazer, 2005). For dementia incidence, one study found that literacy level was predictive of dementia in both races (Kaup et al., 2014). These studies suggest that literacy level as an important consideration for racial disparities in Alzheimer's disease risk that may help to account for more of the discrepancy in risk than education alone.

Educational quality. Three studies identified in this review examined markers of school quality (e.g. student-teacher ratios) on cognitive function. One observed an association between school quality and cognitive function that remained after accounting for education and literacy level (Crowe, et. al., 2013). The association did not differ by race, but was only present in those with a high school education or less (Crowe et al., 2013). A second study found that school quality, years of education and late-life literacy each were associated with cognitive function in AAs, while among NHWs there was only an association with late-life literacy and educational quality (Sisco et al., 2015). The third study observed that state of school attendance was associated with cognitive function in both races after accounting for years of education, but the association was stronger in AAs than NHWs in a national sample, and stronger in NHWs than AAs in a New York City sample (Liu et al., 2015). We identified no studies in our search that examined the relationship between educational quality and rate of cognitive decline or incident Alzheimer's disease. Combined, these studies suggest that discrepancies in educational quality in combination with years of education and literacy level likely account for some of the observed racial disparities in Alzheimer's disease risk.

Obesity

We identified 10 studies that examined the effect of obesity on racial differences in cognition. Three studies reported bivariate analysis of BMI by race, all of which found mean BMI is higher in AAs than NHWs (Arvanitakis, Capuano, Bennett, & Barnes, 2018; Bressler et al., 2013; Sturman et al., 2008). Among those studies that examined an association with cognitive function, one study found that being overweight or obese was associated with higher cognitive functioning in AAs but not in NHWs (Rajan, Skarupski, Rasmussen, & Evans, 2014), while two found that obesity was associated with lower cognitive function for AAs, but not NHWs (Bryant, Ford, & Kim, 2014; Sturman et al., 2008). One study observed no association between obesity and cognitive function in either race (Reuser et al., 2011). In studies that examined the effect on rate of cognitive decline, one study observed that higher BMI was protective against decline, and that there was no difference by race (Arvanitakis, et. al., 2018), while another found that the protective effect of obesity was only present in APOE-e4 carriers, regardless of race (Rajan et al., 2014). A third study observed no effect of BMI on cognitive decline in either race (Kaup et al., 2015). A fourth study observed an effect for both races, but only when including those participants who already were cognitively impaired (Sturman et al., 2008). Of the two studies that examined obesity in relation to incident Alzheimer's disease and related dementias, one found that obesity increased the risk of dementia incidence in NHWs, but not AAs (Gottesman et al., 2017) while the second observed a protective effect of obesity for both NHWs and AAs when BMI was equal to 30-34.9, but only for NHWs when BMI was greater than 34.9 (G. Hu et al., 2012).

One additional study that we included in this review examined if 4 alleles associated with the fat mass and obesity gene FTO were associated with cognitive function and decline. The authors reported that while AAs had greater genetic risk of obesity, there were no racial differences in its association with cognitive function, while NHWs with genetic risk of obesity faced increased rate of cognitive decline (Bressler et al., 2013). Our findings reflect the complex relationship between obesity and Alzheimer's disease risk and demonstrate that there is insufficient evidence to determine if and how obesity plays a role in racial disparities for Alzheimer's disease.

Smoking

We identified eight studies that examined the association between smoking and cognitive function or rate of cognitive decline. We did not identify any studies that met our criteria for incident Alzheimer's disease or related dementias. In studies that reported bivariate differences in smoking by race, two studies reported that smokers were more likely to be black (Aggarwal et al., 2006) or black men (Kuczmarski et al., 2015), and one study found smokers were more likely to be white (Knopman et al., 2001). In association with cognitive function, three studies reported no association with smoking (Bachman, Green, Benke, Cupples, & Farrer, 2003; Kuczmarski et al., 2015; Reuser et al., 2011), and one study reported that current smoking was associated with lower cognitive function, but that there was no difference by race (Aggarwal et al., 2006). However, one reported that not smoking, when combined with physical activity, attenuates racial differences in cognitive function by 5% (Vásquez et al., 2015). In analysis of the effect on rate of cognitive decline, one study observed smoking was predictive of cognitive decline in both races (Yaffe et al., 2009), and one study found that smoking was not associated with rate of cognitive

decline in the full sample, but current smokers versus former smokers had faster cognitive decline on one cognitive function test (Knopman et al., 2001). Two additional studies observed no association between smoking and rate of cognitive decline for either race (Kaup et al., 2015; Vásquez et al., 2015). Combined, these studies provide an inconclusive picture of whether smoking contributes to racial disparities.

Physical Activity

We identified seven studies were identified that examined the role of physical activity in relation to cognitive function and rate of cognitive decline. We did not identify any studies that compared AAs to NHWs in the effect of physical activity on incident Alzheimer's disease. In the five studies that reported bivariate associations by race, all reported that AAs were less likely to participate in moderate and/or vigorous physical activity than NHWs (Masel et al., 2010; Rajan et al., 2015; Vásquez et al., 2015; Zhu et al., 2015, 2017). In adjusted analysis for cognitive function, one study observed a protective effect for physical activity that did not vary by race (Zhu et al., 2015), and two studies observed that physical activity partially mediated racial differences in cognitive function (Masel et al., 2010; Vásquez et al., 2015). By contrast, one study found that for AAs the effect of engaging in 1.25-3.99 hours of physical activity per week was similar to that of engaging in >4 hours of physical activity per week for NHWs, suggesting a stronger protective effect of physical activity for AAs (Rajan et al., 2015). Rate of cognitive decline was analyzed in four studies, two of which observed a protective effect of physical activity only among NHWs (Rajan et al., 2015; Zhu et al., 2017), one that found the protective effect did not vary by race (Yaffe et al., 2009), and one that found no association in either race (Kaup et al., 2015). These findings suggest that lower physical activity may help to

explain some of the differences by race in cognitive function scores, but there is insufficient evidence to know if physical activity contributes to racial disparities in cognitive decline.

Psychosocial Stress

We identified six studies that examined racial differences in the association of psychosocial stress and cognition. Examples of stress measures were items from the Perceived Stress Scale (Aggarwal, et. al. 2014), recent major negative life events (Kaup, et. al. 2015; Sheffler, et. al. 2014), or self-reported lifetime stressful experiences (Zuelsdorf, 2017), (Aggarwal et al., 2014; Kaup et al., 2015; Sheffler et al., 2014; Zuelsdorff et al., 2017). In bivariate analysis, three studies reported a higher number of stressful events among AAs compared with NHWs (Aggarwal et al., 2014; Wilson, Bennett, et al., 2005; Zuelsdorff et al., 2017), and one observed comparable levels of stress between AAs and NHWs (Wilson, Barnes, et al., 2005). One study examined the association with cognitive function, finding that the negative effect of stress on cognitive function was stronger for AAs (Zuelsdorff et al., 2017).

Higher levels of stress were associated with faster rate of cognitive decline in four studies (Aggarwal et al., 2014; Kaup et al., 2015; Sheffler et al., 2014; Wilson, Bennett, et al., 2005). There was no difference by race in two studies (Aggarwal et al., 2014; Wilson, Bennett, et al., 2005), but a third study observed that stress only mattered for cognitive decline in NHWs (Kaup et al., 2015). The fourth study found that the rate of cognitive decline was greater among AAs when stress was low, but that there was no difference in rate of decline between AAs and NHWs when stress was high (Sheffler et al., 2014). For incident Alzheimer's disease, one study found that stress was predictive of Alzheimer's disease for NHWs, but not AAs (Wilson, Barnes, et al., 2005). These findings suggest that psychosocial stress may be an important risk factor for

Alzheimer's disease, though there is insufficient evidence to determine if it helps to explain racial disparities.

Social Isolation

We identified six studies that examined the relationship between social isolation and our cognitive outcomes, though each study measured isolation using different tools and conceptualizations (e.g., self-reported loneliness, measures of degree and types of interpersonal support and social network size). Among studies reporting bivariate associations of isolation and race, one reported slightly higher levels among AAs (Kats et al., 2016), one reported higher levels of isolation among NHWs (Han, Capuano, Barnes, & Bennett, 2016), and a third study observed no difference in prevalence of isolation by race (Zahodne, Watson, Seehra, & Martinez, 2017). In studies that examined the relationship with cognitive function, three studies found isolation was associated with lower cognitive function, but observed no difference in the effect by race (Han et al., 2016; Kats et al., 2016; Zahodne et al., 2017).

In those examining the rate of cognitive decline, one study reported that frequency of social contact is more protective for NHWs than AAs, but that the number of social ties produced no difference in effect by race (Barnes, Mendes de Leon, Bienias, & Evans, 2004). Three studies observed no effect of isolation on rate of cognitive decline in either race group (Kats et al., 2016; Kaup et al., 2015; Yaffe et al., 2009). We did not identify any studies that compared the effect of social isolation on incident Alzheimer's disease or related dementia by race. Broadly, these findings suggest that while social isolation and cognitive function are associated, there is insufficient evidence to determine if social isolation plays a role in racial disparities in any of the cognitive outcomes.

Discussion

We found strong evidence that years of education and literacy help to explain disparities in Alzheimer's disease (AD) risk between NHWs and AAs across measures of cognitive function, rate of cognitive decline and incident AD. We found moderate evidence that school quality and physical activity may help to explain racial disparities in cognitive function. We observed weak or inconclusive evidence for obesity, psychosocial stress, smoking or social isolation in explaining racial disparities in AD risk across all measures of cognition.

Delineating these findings by cognitive function at a single time point, rate of cognitive decline, and incident AD is important to understanding and intervening on racial disparities. Some studies have reported that AAs tend to have lower cognitive function scores, though their rate of cognitive decline is equal to, or slower than NHWs (Early et al., 2013; Masel & Peek, 2009; Weuve et al., 2018). As such, the disparities observed might not be due to faster decline over time among AAs, but lower baseline cognition that results in increased AD incidence at an earlier age, as exemplified in Figure 2. Different interventions at different points in the life span may therefore help to address racial disparities. Early life interventions may help reduce disparities in baseline differences for the next generation. Later in life, interventions that slow the rate of decline may preserve cognitive functioning and lower the risk of AD.

About half of the studies in this review focused on the effect of one or more of the six social and behavioral risk factors on cognitive function at a single point in time. While these associational studies may suggest important factors that contribute to differences in baseline cognitive functioning, it is also possible that 1) the risk factors are the result rather than cause of lower or declining cognitive function, or 2) that the observed associations are driven by a third

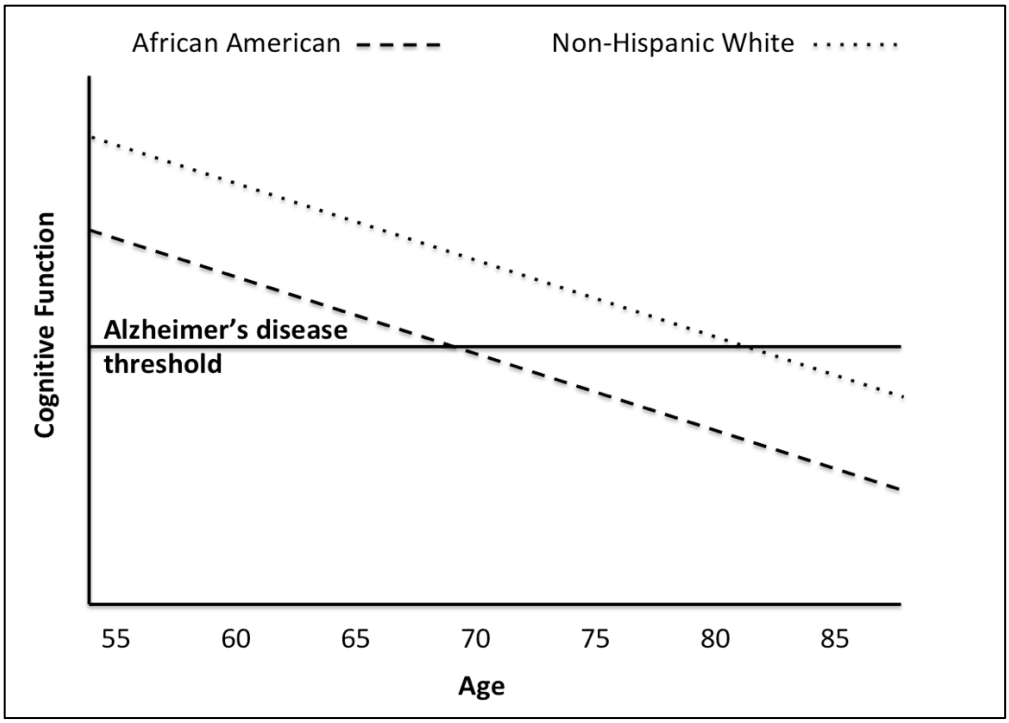

FIGURE 2. *Hypothetical AD incidence by race based on baseline cognition.*

variable. For example, all 3 of the studies that tested the association of social isolation measured it at the same time as cognitive function (Han et al., 2016; Katz et al., 2012; Zahodne et al., 2017), and the 3 studies assessing the impact of physical activity on cognitive function measured it at the same time or within 6 months of cognitive assessment (Masel et al., 2010; Vásquez et al., 2015; Zhu et al., 2015). It is possible that both social isolation and exercise were determined by, rather than predictive of, changes in cognition. Alternatively, cognitive function, social isolation and physical activity may all be influenced by a third variable, such as depression.

By contrast, most of the studies in this review that analyzed rate of cognitive decline had years-long gaps between baseline risks and cognitive testing and adjusted for one's own baseline scores on cognitive function. These studies provide a stronger evidence base for factors that

could play a role in how rapidly one's cognition declines, thereby indicating possible opportunities for late-in-life interventions to reduce the risk of AD. Years of education and literacy were the only risk factors examined in this review with consistent evidence in both studies of cognitive function and rate of cognitive decline and/or incident AD.

Another important consideration in study design for this review is the distinction in interpretation of studies that tested for mediation versus moderation to examine racial disparities in the effect of the risk factor on cognitive outcomes. Studies that examined education and/or literacy as a mediator found that differences in cognitive outcomes are partially or fully explained by differences in educational attainment and literacy (Carvalho et al., 2015; Chin et al., 2012; Crowe et al., 2008; Masel et al., 2010; Sachs-Ericsson & Blazer, 2005; Vásquez et al., 2015). Interpreting this finding suggests that the differences in educational attainment and literacy in itself may explain the racial disparity in AD risk. By contrast, one study in this review found evidence for education as a moderator where the beneficial effect of having more than a high school degree was stronger for AAs than NHWs (Barnes et al., 2011). This finding suggests disparities are not merely the result of direct effects of education attained early in life, but that other factors associated with these differences in education may accumulate to enhance the effect of education on AD risk, such as income, occupational status, or the stress experienced from racial discrimination. Studies identified by this review that formally tested for moderation were a minority, indicating a critical gap in the literature, as many different social, behavioral, environmental and biological factors likely interact in producing aging-related disparities (C. V. Hill et al., 2015; McDonough & Allen, 2018). This difference in study design and interpretation

indicates different possibilities in testing and understanding the possible biological mechanism(s) of the education-AD relationship.

Promising Frameworks for Exploring Education and Alzheimer's Disease Risk

One of the leading theories to explain the link between education and literacy to Alzheimer's disease broadly is the cognitive reserve hypothesis. The concept of cognitive reserve emerged to help explain why some individuals have fewer clinical symptoms of Alzheimer's disease in the presence of neuropathology compared with others (Stern, 2012). Indeed, some studies that have investigated racial differences in AD pathology in autopsied brains have failed to find clear differences between NHWs and AAs (Riudavets et al., 2006; Sandberg, Stewart, Smialek, & Troncoso, 2001). The hypothesis posits that cognitive stimulation throughout one's life will allow for greater neurocognitive compensation and flexibility, which results in fewer cognitive symptoms when Alzheimer's disease pathology is present (Stern, 2009). The relationship between education and cognitive reserve is assumed to result from greater cognitive stimulation – especially at early ages when the brain is in critical phases of development (Lesuis et al., 2018). While the exact effect of cognitive reserve on brain structure remains an open question, some recent research has found that individuals with higher cognitive reserve had slower early cognitive decline despite gray matter atrophy (Mungas et al., 2018). One study found those with higher cognitive reserve were able to more efficiently activate neural networks needed to perform a range of cognitive tasks (e.g. memory, executive functioning) (Stern, Gazes, Razlighi, Steffener, & Habeck, 2018). Another study found that those with higher cognitive reserve did not require the same high levels of activation and synchronization of neural networks in order to perform memory tasks (Martínez et al., 2018). Combined, these studies

suggest that those with cognitive reserve have increased neuro-functioning, yet do not require this efficiency to effectively perform cognitive tasks. While these studies are enlightening, the cognitive reserve hypothesis is based on using education, literacy, IQ as proxies of reserve, under an assumption that these proxies represent an effect of cognitive stimulation (Valenzuela & Sachdev, 2006). However, in most other examinations of the link between education and health disparities, education is often presumed to operate indirectly through its influence on psychosocial wellbeing, access to resources and health behaviors (Adler & Stewart, 2010a).

As such, an alternative biological mechanism that may help to explain the relationship between education and AD risk is "weathering." The weathering hypothesis argues that the stressful experiences of racial discrimination and oppression contribute to faster biological aging (Geronimus, 1992; Geronimus et al., 2006). The concept was initially proposed as the mechanism to explain why racial disparities in pre-term birth persist among college-educated AA mothers compared to college-educated NHW mothers – a pattern that challenged the notion that racial disparities were driven largely by socioeconomic disparities (Geronimus, 1992). Weathering is presumed to operate via chronic stress and the over-activation of the hypothalamic pituitary adrenal axis and the sympathetic adrenal medullary axis – also known as the "fight or flight" response (Booth et al., 2015; McEwen, 2012; Seeman, McEwen, Rowe, & Singer, 2001). As a result, chronic stress produces multiple changes to the metabolic, inflammatory and cardiovascular systems (i.e. allostatic load) that may increase Alzheimer's disease risk both directly through the influence on cognition, and indirectly through its influence on cerebrovascular health (Juster et al., 2010; McEwen, 2012; Snyder et al., 2015). Allostatic load may also contribute directly to neuroinflammation, resulting in neuronal death and increased risk

of AD (Levy Nogueira, Epelbaum, Steyaert, Dubois, & Schwartz, 2016). Thus, the weathering hypothesis could help to explain the finding that education may have a stronger effect on AA cognition than NHW in that the socioeconomic factors associated with lower stress (e.g. income, safe housing and communities, etc.) may be more strongly tied to higher education for AAs than for NHWs.

It is important to note that the limited evidence in this review for psychosocial stress as an explanatory factor for racial disparities in AD does not preclude "weathering" and chronic stress as possible mechanism. The inconsistent findings were from few studies that used various measures of stress, suggesting more research on weathering and allostatic load might help to clarify the mechanistic pathways racial disparities in Alzheimer's disease. To date, few studies have looked at the effects of allostatic load and cognitive reserve in concert. To move this research forward, new studies might investigate if and how the concept of allostatic load contributes to our understanding of cognitive reserve, and if the effects of cognitive stimulation and chronic stress interact to influence brain structures and neural processes that counter or reinforce cognitive changes. We also need broader exploration of how multiple levels of factors may accumulate or interact to drive racial disparities in AD, as outlined in the NIA Health Disparities Research Framework (C. V. Hill et al., 2015). Accomplishing this task will require collaborative efforts between neurologists, epidemiologists and social scientists to explore to define the relationships and test interventions that may reduce Alzheimer's disease risk through the identified pathways.

Limitations

This review has several limitations of note. First, we chose to focus on epidemiological studies in an effort to gain a better understanding of the "real life" population distributions of multiple potentially modifiable risk factors. The trade-off of this approach is that all of the evidence identified in this review is observational and associational, limiting causal interpretation from the reviewed findings. Additionally, in an effort to narrow our scope, we based our searches around Alzheimer's disease, cognitive function and rate of cognitive decline as the key outcomes, which did not identify studies focused exclusively on vascular or other types of dementia that also have racial differences and could have contributed to our analysis and interpretation of findings. We also were unable to differentiate or highlight the findings for specific cognitive domains pertinent to AD risk, such as episodic memory and executive functioning, as most of the studies in this review did not report their findings by cognitive domain. This more nuanced approach may have enabled us to detect more specific patterns between the selected risk factors and racial disparities in AD.

We were further limited by the geographic dispersion of available studies. While we did not limit our search geographically, nearly all of the cohorts used in the included studies resided in the south, or the industrial northeast/Midwest; both regions have histories of migration and race-based laws and practices that are distinct from other regions, reducing generalizability. Studies that explore mechanisms of racial disparities in Alzheimer's disease and its risk factors with nationally representative cohorts, cohorts residing in the West, and younger cohorts could enhance our findings.

Conclusions

As detailed by Hill, et. al. (2015), health disparities rarely are the product of singular factors, but rather emerge throughout the life course from a constellation of factors that interact across multiple domains (environmental, sociocultural, behavioral, and biological), (C. V. Hill et al., 2015). It is generally recognized that the development of AD requires both a biological risk, such as genetic predisposition, in addition to modifiable risks embedded within environmental, sociocultural and behavioral contexts (McDonough & Allen, 2018). This review synthesized the evidence on modifiable factors that may be distributed differently by race group and that have been linked to AD risk in the general population. These factors map onto the environmental, sociocultural and behavioral domains of the NIA Health Disparities Research Framework, but are far from a comprehensive list of possible factors that could contribute to racial disparities in AD (C. V. Hill et al., 2015).

Regardless of the multitude of factors likely at play, however, at the root of all health disparities is the embodiment of social inequality (Ferraro & Shippee, 2009; Krieger, 2005). In the context of education, literacy and AD risk, racial discrimination in the form of Jim Crow laws has contributed to the lower educational attainment – and by extension literacy – for many AA older adults in the studies reviewed. Education is associated broadly with health behaviors and improved access to health promoting economic, physical and psychosocial resources (Cutler & Lleras-Muney, 2010; Ross & Wu, 1995). Although the de jure segregation of past generations is fortunately in the past, de facto residential segregation and other forms of racism – and their associated effects on education – continue to persist in the U.S. (Kotok, Frankenberg, Schafft,

Mann, & Fuller, 2017; Massey & Denton, 1993; Rugh & Massey, 2014). This likely shapes AD risk and disparities for the next generation.

While our findings identified major gaps in knowledge regarding the role of modifiable risk factors in racial disparities, they also provide direction for future research to disentangle the root causes of these disparities and opportunities for risk reducing intervention and policy efforts. Considering the strong evidence for education and its possible mechanisms, it is especially important to consider both early and late-life interventions surrounding cognitive stimulation and chronic stress at individual, community and policy levels to reduce racial disparities in Alzheimer's disease risk.

CHAPTER 3: STATE INEQUALITY, SOCIOECONOMIC POSITION AND SUBJECTIVE COGNITIVE DECLINE IN THE UNITED STATES

Background

Over the past several decades, researchers have observed a "social gradient in health" where each step down on the social ladder is associated with worse health outcomes – even when comparing different status levels of middle-class office workers (Marmot et al., 1991). This growing body of literature has demonstrated that the influence of socioeconomic position (SEP) on health outcomes is not merely due to the material deprivation among those living in poverty, but may be attributed, in part, to status rankings between individuals (Marmot, 2004; Wilkinson, 1999). Known as the "relative income hypothesis," this pattern in health outcomes is theorized to operate through a psychosocial/stress response to social comparisons (Mullahy et al., 2011). Additional studies suggest that individuals in societies with higher levels of income inequality may experience an increased sense of social comparison, or "status anxiety," such that income inequality may be an important independent risk factor for health conditions with social gradients beyond what is accounted for by the individual's SEP (Pickett & Wilkinson, 2015).

The association between income inequality and health has been replicated in cross-national comparisons, and in studies that examine differences between U.S. states for a variety of health conditions (Kim, Kawachi, Hoorn, & Ezzati, 2008; Pickett & Wilkinson, 2015; Van Deurzen, Van Ingen, & Van Oorschot, 2015). The status anxiety hypothesis suggests that rising inequality has a direct effect on health via its activation of the body's stress-response system, which produces worse health outcomes (Beckie, 2012; Kondo, Kawachi, Subramanian, Takeda, & Yamagata, 2008; Mishra & Carleton, 2015; Singh-Manoux et al., 2003). However, debate

continues over if and how income inequality may affect individual health above the effects of individual SEP. Several proposed mechanisms may help to explain observed relationships, including the differences in social spending on education and health care, and social support for public health that may prevail in more economically equal societies (Kawachi & Kennedy, 1999). The inequality-health relationship has been observed for a variety of health conditions that could be influenced by stress-response, including life expectancy, cardivascular health and mental health (D. Kim et al., 2008; Pickett & Wilkinson, 2015; Van Deurzen et al., 2015). To our knowledge, no one has examined the effect of income inequality on age-related cognitive decline or dementia, though there are pertinent theoretical and practical reasons to do so.

More than 5 million people in the U.S. have been diagnosed with Alzheimer's disease, the most common type of dementia, and it is estimated this will increase to 11.6 million by 2025 (Hebert et al., 2013). As the number of people living with dementia increases, the demand for dementia care services to help with the declines in cognition and independent functioning that are part of the disease is expected to continue to outpace the capacity of medical and long-term care systems, with substantial financial and health impacts to individuals, families and society (Alzheimer's Association, 2018; De Vugt & Verhey, 2013; Plassman et al., 2007; Richardson et al., 2013; World Health Organization, 2012).

Dementia is typically diagnosed through a clinical assessment of changes in cognition that begin to substantially interfere with one's ability to fulfill their daily activities. However, dementia is at the severe end of a continuum of age-related cognitive decline that often begins with self-identified changes in cognitive functioning, or subjective cognitive decline (SCD). SCD may not be detectable by a clinical screening test, though it is increasingly recognized as a

reliable predictor of objectively assessed cognitive decline, including among those with higher levels of education who tend to perform better on clinical assessments (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007). Though not all cases of SCD or clinically detectable cognitive decline will progress to dementia, SCD can have meaningful impacts on functional abilities and serves as an important early identifier of those most at risk for dementia (Kaduszkiewicz et al., 2014; Marcos et al., 2016; Mitchell & Shiri-Feshki, 2009; Taylor, Bouldin, & Mcguire, 2018).

A social gradient has been observed for age-related cognitive decline by occupational status and income, though some studies note that these associations are substantially attenuated or nullified after accounting for the effect of education (Anttila et al., 2002; Karp et al., 2004; Staff, Chapko, Hogan, & Whalley, 2016; Zeki Al Hazzouri, Haan, Galea, & Aiello, 2011). Educational attainment is one of the best documented modifiable risks for age-related declines in cognition, and has been shown to have a dose-response relationship with clinically-assessed cognitive outcomes (Beydoun et al., 2014; Xu et al., 2016). The body of evidence for the relationship between cognitive decline and education has largely pointed to a direct effect of cognitive stimulation resulting from education as the underlying mechanism for better late-life cognitive outcomes (Carvalho et al., 2015; Jefferson et al., 2011; Meng & D'Arcy, 2012). Cognitive stimulation is hypothesized to have a protective effect for cognition through promoting "cognitive reserve," or the increased efficiency and capacity of neural networks in the presence of dementia pathology (Stern, 2009). Theoretically, cognitive stimulation is thought to allow for greater cognitive flexibility that allows an individual to continue to function well, even in the presence of dementia-related brain pathologies (Martínez et al., 2018; Meng & D'Arcy, 2012).

However, it is plausible that the effects of education and other markers of SEP on cognitive decline could operate in part through status anxiety. Theoretically, status anxiety contributes to the over-activation of the body's stress response and can result in physiological damage operationalized through a composite of biomarkers that measure allostatic load (McEwen, 2012; Wilkinson & Pickett, 2017). Importantly, allostatic load has direct neurocognitive influences on memory and cognitive functioning that may contribute to the risk of Alzheimer's disease (Booth et al., 2015; Juster et al., 2010; Lesuis et al., 2018). Examining the relationship between cognitive decline, inequality and individual markers of SEP may therefore help to shed light on the underlying mechanism between the SEP-cognitive decline relationship, and provide additional evidence for or against the role of inequality in health, and the debated status anxiety hypothesis.

The aim of this study was to test for an association between subjective cognitive decline (SCD) as an early predictor of dementia risk, measures of individual SEP, and state-level income inequality in the U.S. We hypothesize finding evidence for status anxiety hypothesis via presence of a social gradient in markers of individual SEP, and that higher state-level income inequality will be associated with higher odds of SCD after controlling for individual-level SEP. Additionally, this study conducted a secondary examination of status anxiety by modeling an interaction between individual income and income inequality to see if those with lower household income would be negatively affected by income inequality to a greater degree than those with higher household income. Theoretically, a social gradient in the markers of SEP – especially income – and a relationship between income inequality and cognitive decline would support the hypothesis that income inequality impacts health through the psychosocial pathway

of status anxiety. If these relationships are not observed, alternative mechanisms should be considered to explain the observed social gradients in health, which for cognitive decline and Alzheimer's disease risk may be cognitive stimulation.

Methods

Data Sources

We used the Cognitive Decline module from the 2015 and 2016 Behavioral Risk Factor Surveillance System (BRFSS). The BRFSS is a cross-sectional telephone survey conducted annually by the United States Centers for Disease Control and Prevention that collects self-reported health information from community-dwelling adults (Centers for Disease Control and Prevention, 2016b). The cognitive decline module was asked of all participants age 45 or older who resided in a state that elected to participate in the module. All states except Pennsylvania and Washington D.C. participated in the cognitive decline module in 2015 or 2016. New Jersey, New York, Oregon, Tennessee and Utah participated in the cognitive decline module in both years; for these states we included only the 2016 participants, providing a total of 50 clusters (49 states and Washington D.C.). Puerto Rico participated in 2015, but was excluded from analysis because it is an outlier on our key variables of interest; Puerto Rico has substantially lower household income (median US$19,606) and slightly higher income inequality (Gini coefficient=0.542; U.S. state min/max=0.408, 0.535) than any U.S. state (United States Census Bureau, 2016).

Subjective Cognitive Decline

The primary outcome of this study was the dichotomized response to an item measuring subjective cognitive decline (SCD), obtained from the BRFSS cognitive decline module.

Participants were classified as having SCD if they responded yes to the question: “During the past 12 months, have you experienced confusion or memory loss that is happening more often or is getting worse?”

Individual Socioeconomic Position

We used variables from the BRFSS for household income, education and home ownership as markers of SEP. Income was provided in 8 categories ranging from <$10,000 to ≥$75,000; the highest income category was modeled as the reference. Education was categorized as less than high school, high school graduate, some college or technical school, and college or technical school graduate, with the highest education category as the reference. Homeownership was modeled as a dichotomous variable with owners as the reference.

State-level Income Inequality

As a measure of states’ income inequality, we used the Gini coefficients based on the 2015 and 2015 American Community Survey (ACS), an annual survey of about 3.5 million households (United States Census Bureau, 2015). This indicator, published by the U.S. census bureau, is one of the most commonly used measures of income inequality. Its value ranges from 0 (complete equality) to 1 (one household captures all income); (De Maio, 2007).

Individual Covariates

Adjusted models controlled for gender, age and race/ethnicity, provided by the BRFSS. Race/ethnicity was categorized as non-Hispanic white (reference), non-Hispanic black, Hispanic/Latino, Asian, and an “other” category comprised of respondents who reported their race as American Indian/Alaska Native, Pacific Islander/Hawaiian, mixed race or other. Age was

modeled categorically at 45-49 (reference); 50-59; 60-69; 70-79; and top-coded at ≥80 years, as available in the BRFSS.

Statistical Analysis

We matched the 2015 and 2016 BRFSS datasets with 2015 and 2016 income inequality data from the ACS, respectively (United States Census Bureau, 2015, 2016). In the primary analysis, we included participants of the cognitive decline module who had valid responses for age, sex, race/ethnicity, education, home-ownership and income. We calculated weighted proportions of demographic and health characteristics of participants based on SCD status and used chi-square tests to compare the demographic characteristics of those with SCD to those without SCD.

To test for the effects of individual SEP and state-level income inequality on SCD, we used a Generalized Estimating Equation (GEE) with a logit link and independent working covariance, clustered by the participant's state of residence to fit unadjusted and adjusted models. Using a GEE model allowed us to specify the nested nature of the data within each U.S. state and account for heterogeneity of income inequality between states. The GEE provides an average estimate of effect of SCD for the population. This interpretation is in contrast to multilevel models, which estimate the effect for a specific participant, conditional on the covariates in the model, including the state (Hubbard et al., 2010). Some methodologists argue that the population averaged model (GEE) is more appropriate when the research question focuses on neighborhood or state effects (Hubbard et al., 2010).

We tested for effect modification of household income grouped at 3 levels with state-level income inequality to examine if the impact of income inequality varies depending on one's

income, by including an interaction term. We also performed two sensitivity analyses. First, we recalculated our analysis use lagged Gini coefficients from 2005 and 2010, computed by the Census Bureau based on 5 years of ACS data (United States Census Bureau, 2015). While these models are more likely to result in state level misclassification (individuals are more likely to move between states within 5 years or 10 years than 1 year), it also has the strength of capturing the contextual effect of income inequality, which may take years to influence health. Second, we conducted multiple imputation using chained equations to account for the high degree of missing data on income. Of the 223,985 participants of the SCD module in 2015 and 2016, 2.1% were missing information on education, race, homeownership or sex, and 15.4% were missing household income data. We performed 200 imputations with all variables from the primary model. We also included variables from the BRFSS dataset that are conceptually or empirically linked with missing income data and that were correlated with income at ≥ 0.3: internet use in the past 30 days, 30-day self-reported health, marital status and employment status (Azur, Stuart, Frangakis, & Leaf, 2011).

Appropriate population weights provided by the BRFSS were applied in all models following guidance available on the BRFSS website (Centers for Disease Control and Prevention, 2016a). Application of these weights adjusts each state's participant sample, so it is representative of its population. All analyses were conducted in Stata 14.2 (College Station, TX).

Results

Of the 223,985 who completed the cognitive decline module, 184,633 had complete data and were included in the primary analyses (Figure 3). On average, participants who were older, had less than a college or technical school education, were not non-Hispanic white or Asian and

were not homeowners were more likely to report SCD (Table 5). Additionally, 52.1% of those without SCD reported a household income of more than $50,000 a year, compared to 30.2% of those with SCD.

In the primary analysis, we did not find a statistically significant association between state-level income inequality and SCD, though the odds ratio was in the direction predicted. In unadjusted analysis, the odds of SCD increased 1.2 (95% CI: 0.9, 1.5; p=0.18) times for each 0.1 unit increase in income inequality, as measured by the Gini coefficient (Table 6). Similarly, in adjusted analyses, the odds ratio for income inequality was 1.2 (95% CI: 0.9, 1.6; p=0.28). The predicted probability of SCD for those in the most equal state (Gini=0.408) was 0.09, compared to the least equal state (Gini=0.535) at 0.11. Overall, the change in predicted probabilities for or every .05 unit increase in the Gini coefficient resulted in less than a 1%-point increase in the predicted probability of SCD, when all covariates were at their mean levels. However, all three measures of SEP (household income, education and home ownership) were protective for SCD.

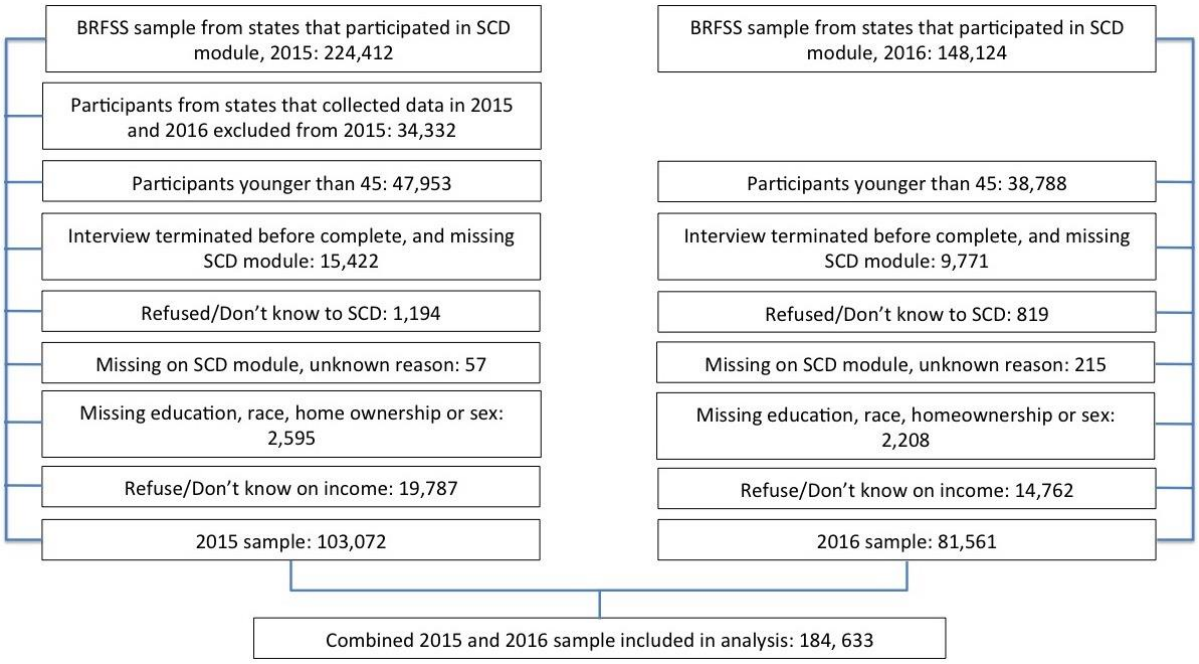

FIGURE 3. *Inclusion and exclusion criteria for the primary analysis.*

TABLE 5. *Demographic characteristics of included BRFSS participants.*

	SCD N=19,662	**No SCD N=164,971**	**p-value[2]**
	Weighted %	**Weighted %**	
Household Income ($US)			
≥$75,000	6.0	94.0	<0.001
≥$50,000 & <$75,000	8.6	91.4	
≥$35,000 & <$50,000	10.4	89.6	
≥$25,000 & <$35,000	13.7	86.3	
≥$20,000 & <$25,000	15.3	84.7	
≥$15,000 & <$20,000	17.4	82.6	
≥$10,000 & <$15,000	21.2	78.8	
<$10,000	26.3	73.7	
Years of Education			
College Graduate	7.0	93.0	<0.001
Some College	11.5	88.5	
High School Graduate	11.8	88.2	
Less than High School	18.7	81.3	
Homeowners	10.0	90.0	<0.001
Non-homeowners	17.4	82.6	
Female	11.1	88.9	0.55
Male	11.4	88.6	
Age			
45-50	9.7	90.3	<0.001
50-59	11.1	88.9	
60-69	10.4	89.6	
70-79	11.9	88.1	
80+	16.6	83.4	
Race/Ethnicity			
Non-Hispanic White	10.9	89.1	<0.001
Non-Hispanic Black	13.0	87.0	
Hispanic	11.6	88.4	
Asian	6.0	94.0	
Other	17.6	82.4	

[1]Self-reported experience with confusion or memory loss that is happening more often or getting worse in the last 12 months.
[2]X^2 test, adjusted for sampling weights

TABLE 6. *Associations of state-level income inequality, SES and SCD**

	2015-2016 Gini, matched to BRFSS year		
	OR	**95% CI**	**p-value**
State income inequality (unadjusted)[t]	1.19	0.92, 1.56	0.19
State income inequality(adjusted)[t]	1.19	0.87, 1.62	0.281
Household Income			<0.001
≥$75,000	Ref		
≥$50,000 & <$75,000	1.40	1.26, 1.56	
≥$35,000 & <$50,000	1.67	1.53, 1.83	
≥$25,000 & <$35,000	2.22	1.91, 2.58	
≥$20,000 & <$25,000	2.50	2.11, 2.98	
≥$15,000 & <$20,000	2.81	2.35, 3.37	
≥$10,000 & <$15,000	3.52	3.97, 4.17	
<$10,000	4.66	3.79, 5.74	
Education			<0.001
College or technical school graduate	Ref		
Some college	1.30	1.22, 1.39	
High school graduate	1.12	1.04, 1.21	
Less than High School	1.51	1.36, 1.68	
Non-homeowners	1.19	1.07, 1.33	0.002

Adjusted ORs control for age, race and sex.
[t]OR is based on a 0.1 unit change in Gini coefficient.
[*]Subjective Cognitive Decline: self-reported experience with confusion or memory loss that is happening more often or getting worse in the last 12 months.

Our results for household income reflected a social gradient in health, with an increasing step-wise protective effect for each higher income category. Compared to those with a household income of more than $75,000 a year, participants with household incomes between $50,000 and $75,000 were 1.4 (95% CI: 1.3, 1.6) times more likely to report SCD, while those with household incomes of less than $10,000 per year were 4.7 (95% CI: 3.8, 5.7) times more likely to report SCD. Higher education also was a protective factor for SCD, though the pattern was not

consistent. Compared with college or technical school graduates, those with less than high school had the highest odds of SCD at 1.5 (95% CI: 1.4, 1.7) times, high school graduates had 1.1 (95% CI: 1.0, 1.2) times the odds, and those with some college or technical school had 1.3 (95% CI: 1.2, 1.4) times the odds. Compared with homeowners, those who rented or had another living arrangement were 1.2 (95% CI: 1.1, 1.3) times more likely to report SCD.

We found no evidence of effect modification between income inequality and household income, indicating that the effect of income inequality on SCD does not vary by household income level (Table 7). Additionally, our sensitivity models that examined separately the effect of the ACS 5- and 10-year lagged Gini coefficients produced comparable results to our original findings (Table 8). The results of our multiple imputation sensitivity analysis were also comparable to our primary analysis (Table 9), indicating the robustness of our findings in spite of substantive missing data on income.

Discussion

Summary of Findings

The primary objective for this study was to examine the relationship between state-level income inequality, markers of individual SEP and SCD. We hypothesized that income inequality would be positively associated with SCD after accounting for individual-level SEP. We did not observe a statistically significant relationship between state-level income inequality and SCD in the models tested. While the effect was in the direction predicted, it was substantively small and statistically insignificant. However, we did observe a clear and statistically significant social gradient in health where odds of SCD decreased for each step higher of household income. We

TABLE 7. *Interactive effects of income inequality and SES on SCD*.*

	OR	95% CI	p-value
State income inequality[t]			0.43[1]
≥*$75*,000	1.18	0.74, 1.90	
≥$35,000 & <$75,000	1.40	0.80, 2.44	
<$35,000	1.12	0.86, 1.45	
Education			<0.001
College or Technical School Graduate	Ref.		
Some College	1.30	1.22, 1.39	
High School Graduate	1.15	1.05, 1.25	
Less than High School	1.67	1.49, 1.87	
Non-homeowners	1.30	1.17, 1.45	<0.001

Model controls for age, race and sex.
[t]OR is based on a 0.1 unit change in Gini coefficient.
[*]Subjective Cognitive Decline: self-reported experience with confusion or memory loss that is happening more often or getting worse in the last 12 months.
[1]P-value for the test of the state income inequality by household income.

also observed significant positive associations for SCD with homeownership and higher education.

TABLE 8. *Comparison of effects using lagged state-level income inequality measures.*

	2015-2016 Gini, matched to BRFSS year			Gini: 2010-2015 average			Gini: 2005-2010 average		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
State income inequality[ŧ]	1.19	0.87, 1.62	0.281	1.19	0.86, 1.64	0.295	1.15	0.85, 1.56	0.349
Household Income									
≥$75,000	Ref			Ref			Ref		
≥$50,000 & <$75,000	1.40	1.26, 1.56		1.40	1.26, 1.56		1.40	1.26, 1.55	
≥$35,000 & <$50,000	1.67	1.53, 1.83		1.67	1.53, 1.83		1.67	1.52, 1.83	
≥$25,000 & <$35,000	2.22	1.91, 2.58	<0.001	2.22	1.91, 2.58	<0.001	2.22	1.91, 2.58	<0.001
≥$20,000 & <$25,000	2.50	2.11, 2.98		2.51	2.11, 2.98		2.50	2.10, 2.98	
≥$15,000 & <$20,000	2.81	2.35, 3.37		2.81	2.35, 3.37		2.81	2.34, 3.37	
≥$10,000 & <$15,000	3.52	3.97, 4.17		3.52	2.97, 4.17		3.52	2.96, 4.17	
<$10,000	4.66	3.79, 5.74		4.66	3.79, 5.74		4.66	3.78, 5.74	
Education									
College or technical school graduate	Ref		<0.001	Ref		<0.001	Ref		<0.001
Some college	1.30	1.22, 1.39		1.30	1.22, 1.39		1.30	1.22, 1.39	

High school graduate	1.12	1.04, 1.21		1.12	1.04, 1.21		1.12	1.04, 1.21	
Less than High School	1.51	1.36, 1.68		1.51	1.36, 1.67		1.51	1.36, 1.68	
Non-homeowners	1.19	1.07, 1.33	0.0017	1.19	1.07, 1.33	0.0017	1.20	1.07, 1.34	0.0018

Model controls for age, race and sex.
[t]OR is based on a 0.1-unit change in Gini coefficient

Interpretation

Our findings suggest that income inequality in itself may not have a substantial influence on SCD and dementia risk. This finding reinforces some of the critiques of the income inequality hypothesis. Specifically, critics have argued that any observed relationships between income inequality and health are not likely resulting from a direct effect, but rather income inequality is more likely a mediator in the relationship between other structural processes and health, such as the social distribution of public goods and services (Mellor & Milyo, 2001; Mullahy et al., 2011). Accordingly, many critics also argue that non-psychosocial factors that have a material impact on individual health, such as neighborhood poverty level and race-based residential segregation, may better explain the observed effects (Goldthorpe, John, 2010; Lynch, 2000; Massey & Denton, 1993; Mullahy et al., 2011). Correspondingly, many studies on dementia risk point to the unequal distribution of education across race and class lines as a key explanatory mechanism of disparities in dementia risk, operating via cognitive stimulation (Beydoun et al., 2014; Chin et al., 2012; Crowe et al., 2013; Jefferson et al., 2011; Kaup et al., 2014).

However, while income inequality may not be an important risk factor for SCD, our findings do not preclude the possible role of status anxiety and the psychosocial pathway for individual dementia risk. We observed relatively large and significant differences in odds of

TABLE 9. *Sensitivity analysis comparing the primary and multiple imputation models.*

	Original Model			**Multiple Imputation Model**		
	Coef.	95% CI	p-value	Coef.	95% CI	p-value
State income inequality (unadjusted)[t]	0.18	-0.09, 0.44	0.19	0.30	-0.10, 0.70	0.14
State income inequality (adjusted)[t]	0.17	-0.16, 0.50	0.308	0.26	-0.21, 0.73	0.27
Household Income	-0.19	-0.23, -0.17	<0.001	-0.18	-0.21, -0.15	<0.001
Education	-0.12	-0.20, -0.04	0.004	-0.1	-0.17, -0.03	0.008
Non-homeowners	0.21	0.18, 0.43	<0.001	0.24	0.13, 0.35	<0.001

Model controls for age, race and sex.
[t]OR is based on a 0.1-unit change in Gini coefficient.

SCD, even among those in the top income categories, as would be expected if status anxiety were an operating mechanism. Additionally, our findings for the association between education and SCD suggest that that social status, rather than cognitive stimulation, may be a contributing mechanism for the dementia-education association. Specifically, we observed that graduates of college or technical school and high school fare better than non-completers of either degree. If cognitive stimulation were the dominant mechanism in the relationship between education and dementia risk, as posited by the cognitive reserve hypothesis, more years of education among those who started but did not complete college or technical school should theoretically have a stronger protective effect than what is observed among high school graduates. The effect of education operating as a potential status marker rather than via cognitive stimulation is also supported by findings from some studies from low- and middle-income countries where average

education and literacy levels are low, and there is not a clear link between education and dementia (Chandra et al., 2001; Hall, Gao, Unverzagt, & Hendrie, 2000).

Overall, our findings indicate that dementia risk may not be influenced by income inequality, or exclusively determined by early life factors such as education. Rather, it is possible that the effects of both education and income on dementia risk operate, in part, through social comparisons that may be fueled by resource distribution and other forms of structural inequalities that extend beyond the distribution of income. However, it is also possible that these findings reflect other mechanisms shaped by income and education, such as health behaviors.

Methodological Considerations

The literature linking. income inequality to health is mixed, and frequently dependent upon study design (Kragten & Rözer, 2017), the geographic unit of measurement (Pickett & Wilkinson, 2015), and accurately accounting for the state-level factors that may confound the relationship (Kondo et al., 2009). Our study design and analyses took into account the effect of state context of income inequality, and U.S. states have been observed as sufficiently large and heterogeneous to be sensitive to an effect of income inequality as measured by the Gini coefficient, while counties or cities are often too small to be sensitive to an effect (Bernabé & Marcenes, 2011; Pabayo, Kawachi, & Gilman, 2014; Pickett & Wilkinson, 2015). However, there may be other unmeasured state-level factors that confound the relationship between income inequality and SCD that we could not include in our models, such as state variation in the provision of social services (Bradley et al., 2016). Furthermore, recent research suggests that in some cases the Gini coefficient may not be as sensitive to the effects of income inequality on health as are other markers of inequality, such as the income share of the top 1% or 5% (T. D.

Hill & Jorgenson, 2018). The key difference between income shares and the Gini coefficient is in the ability to account for income inequality at the very top and bottom of the income distribution. Because the Gini coefficient is less sensitive to inequalities at the tail ends of the income distribution, geographies with substantially different income distributions theoretically could have similar Gini coefficients (Palma, 2011).

Limitations

Our study had several limitations. First, we were unable to determine the temporal ordering of the relationship between SCD and markers of SEP due to the cross-sectional design. While educational attainment is often established early in the life course, both income and cognition tend to decline as individuals age. In this study it was impossible to know if SCD predated or contributed to lower income levels, such as through early retirement resulting from cognitive decline. A second limitation was in the restricted availability of household income data. Income in the BRFSS is top-coded at $75,000, limiting our ability to examine if the social gradient we observed between SCD and income continues in a linear fashion for those with income levels above $75,000, or plateaus after a particular threshold of household income. A third key limitation in this analysis was in our inability to account for an adequate lag time or a cumulative exposure of state-level income inequality. While our sensitivity analysis demonstrated similar effects of the Gini coefficient when averaged at 5 and 10 years prior to our outcome, our concern over state misclassification (the BRFSS does not provide information on length of state residence or prior state of residence) discouraged us from examining longer lagged effects that may be influential in dementia risk.

Future Directions

The income gradient and protective effect of completing educational degrees evidenced in this study adds to the body of knowledge for dementia risk, suggesting that income and the effects of status anxiety may be important to consider for dementia risk in addition to the effects of education and cognitive stimulation. Future studies should further examine the role of income inequality, individual SEP and status anxiety on dementia risk in datasets with more explicit measures of perceived social status and employing alternative measures of income inequality. Additionally, cohort studies with available biomarkers for allostatic load or brain imaging would allow for more direct examination and comparison of the effect of individual SEP and income inequality on status anxiety and cognitive reserve as hypothesized mechanisms of dementia risk. A third avenue for exploration is in how the effect of income-based policies and programs throughout the life course shape exposure to income inequality and age-related cognition decline. Already, there is some evidence for a protective effect of late-in-life income beyond the effects of earlier life income for dementia risk (Anttila et al., 2002; Ayyagari & Frisvold, 2015). Future studies could further clarify the role and timing of income-based interventions for reducing the risk of dementia.

In the absence of effective prevention or treatment for dementia, early interventions that target the modifiable risk factors for cognitive decline are the only available strategy for addressing a dementia epidemic (Fink et al., 2018; Livingston et al., 2017). As the population ages and more individuals are at risk of age-related cognitive decline, all plausible possibilities for risk reduction should be considered. A recent report from the Lancet Commission on Dementia Prevention, Intervention, and Care called for researchers and health care providers to

"be ambitious" about dementia by reducing known risk factors (Livingston et al., 2017). Increasing income and lowering chronic stress may prove to be a central and important part of an ambitious approach to reduce the risk of dementia.

CHAPTER 4: SOCIAL STATUS AND STRESS IN RACIAL DISPARITIES IN ALZHEIMER'S DISEASE RISK: AN EXAMINATION OF COGNITIVE RESERVE, STATUS ANXIETY AND WEATHERING

Background

Racial disparities in health have been well established for Alzheimer's disease (AD), with African Americans (AAs) having about 1.5 times the rate of non-Hispanic whites (NHWs) (Mayeda et al., 2016b; Mehta & Yeo, 2016). AD, like many health conditions, involves both biological and social factors in its development. One recent theory described this interaction "seeds and soil," whereby the context of lived experience, including social and physical environments and individual behavior (the soil), determine if genetic risk (a seed) is able to manifest into AD pathology (McDonough & Allen, 2018). While biological variation in risk is an important consideration for individuals from both race groups, by definition *disparities* are those systematic variations in disease rates at the population level that are the product of modifiable social and environmental factors (Gravlee, 2009; Krieger, 2000b).

Link and Phelan (2005) have theorized that the consistent and persistent disparities by social class over time for diseases with distinct etiologies suggests that the social conditions are, in fact, the "fundamental causes" of health disparities (Link & Phelan, 1995; Phelan et al., 2010). This paradigm challenges researchers to think about how those social conditions underlying socioeconomic status and racialized experiences connect in a systematic way to specific disease processes. One hypothesized pathway is the psychosocial effects of "status anxiety." Decades of research on the relationship between SES and various health outcomes have demonstrated the presence of a social gradient where each step higher on the social ladder is associated with

slightly better health (Marmot et al., 1991; Pavalko & Caputo, 2013). When these social gradients are present, the effect of social status on health outcomes is hypothesized to operate through a the psychosocial response to hierarchies and our position within them, referred to as "status anxiety," (Marmot, 2004; Mullahy et al., 2011).

Racial disparities also must be examined beyond the effects of SES, as several studies have found that AAs continue to have poorer health outcomes than NHWs even after accounting for the effects of SES (Geronimus, 1992; Gravlee, 2009; Kawachi et al., 2005). Similar to SES, racial disparities are hypothesized to operate via "weathering," whereby psychosocial processes contribute to the embodiment of racial discrimination and faster aging (Das, 2013; Geronimus, 1992; Geronimus et al., 2006). Both status anxiety and weathering are linked to the detrimental biological effects of chronic stress on physiological functioning and chronic disease risk (Layte & Whelan, 2014; Marmot, 2004; Seeman et al., 2008; Szanton, Gill, & Allen, 2005). Chronic stress contributes to the overactivation of the body's "fight of flight" response, resulting in dysregulation of the metabolic, inflammatory and cardiovascular systems, which contribute to chronic disease risk and accelerated aging (McEwen, 2003; Seeman et al., 2001). The summation of these factors, referred to as "allostatic load" has been linked to Alzheimer's disease risk through its effect on cognitive functioning (Booth et al., 2015; Juster et al., 2010), cerebrovascular health (Snyder et al., 2015), and neuroinflammation and neuronal death (Levy Nogueira et al., 2016). As such, the social conditions that contribute to chronic stress may be critical factors for understanding racial disparities in AD risk.

For AD, very few studies have examined the role of psychosocial processes in explaining racial disparities (see Aggarwal et al., 2014; Kaup et al., 2015; Sheffler, Moxley, & Sachs-

Ericsson, 2014; Wilson, Barnes, et al., 2005; Wilson, Bennett, et al., 2005; Zuelsdorff et al., 2017). Rather, most of the existing evidence currently points to educational attainment in itself as a key explanatory factor (Chin et al., 2012; Dotson et al., 2009; Rodriguez et al., 2018; Sachs-Ericsson & Blazer, 2005; Yaffe et al., 2013). Unlike with the broader literature on health disparities, education is presumed to operate via its direct effect on cognitive stimulation. Neuroimaging studies have shown that higher educational attainment is associated with better cognitive performance, even in the presence of Alzheimer's disease pathology (Meng & D'Arcy, 2012). This finding has given rise to the cognitive reserve hypothesis, which posits that higher levels of education, literacy or other proxies of cognitive stimulation shape neuro-efficiency and help to prevent or delay the onset of disease (Stern, 2009; Stern & Habeck, 2018). This direct effect of education stands in contrast to the interpretation of education operating primarily as a marker of social status and resources (Adler & Stewart, 2010b; Phelan et al., 2010).

This study seeks to expand the understanding of AD disparities in accordance with the broader health disparities literature by clarifying the possible mechanistic pathways between fundamental causes and AD risk. Using path analysis in a diverse national longitudinal cohort of older adults, we aim to examine the possible indirect effect of education through measures of status anxiety and weathering.

Methods

Participants

We used data from the National Social Life and Aging Project, a nationally representative cohort study of older adults and their cohabitating partners (Waite, 2017; Waite, Cagney, et al., 2014; Waite, Laumann, Levinson, Tessler Lindau, & O'Muircheartaigh, 2014). Three waves of

data have been collected at 5-year intervals since 2005. Wave I consists of an initial study cohort of 3,005 individuals born between 1920 and 1947 (Waite, Laumann, et al., 2014). Wave II consists of Wave I participants, as well as their partners and non-respondents from Wave I, comprising a sample of 3,400 (Waite, Cagney, et al., 2014). Wave III continues to follow the surviving Wave I and II participants, and adds a second cohort of individuals born between 1948 and 1965 and their partners, comprising a sample of 4,777 (Waite, 2017). For this study, we used a combined data set from all three waves, limited to NHW and AA participants who have valid cognitive assessment scores in both waves 2 and 3.

Measures

Cognition. We measured global cognition (range 0-20; higher is better cognition) based on data from Waves II (time 1) and III (time 2) of the Chicago Cognitive Function Measure (CCFM), a modified Montreal Cognitive Assessment (MOCA), (Shega et al., 2014). While cognition was measured in all three waves, the Short Portable Mental Status Questionnaire used in Wave I of the NSHAP proved to have a ceiling effect that limited the detection of cognitive deficits or variance in this population (Shega et al., 2014).

Allostatic load. We used six biomarkers collected in Wave II (diastolic and systolic blood pressure, body-mass index, glycated hemoglobin, C-reactive protein and DHEA) that are indicators of cardiovascular, metabolic and inflammatory systems function (Williams, Pham-Kanter, & Leitsch, 2009). Following the method used by Crimmins, et. al. (2003), we used clinically meaningful cutoffs for all biomarkers except C-reactive protein, for which we used an empirical cut-off based on the sample distribution (Crimmins, Johnston, Hayward, & Seeman, 2003). Participants received a score of 1 if they had a value outside of the normal range or above

TABLE 10. *Biomarkers used to calculate allostatic load.*

	Range	**Weighted Mean**	**Cut-point**	**% meeting criteria**	**Determinant of cut-point**
Body-Mass Index	12.5-93.6	29.8	>30	41.20%	clinical
Systolic Blood Pressure	62-226	136.8	>140	39.50%	clinical
Diastolic Blood Pressure	41-125	81.2	>90	19.90%	clinical
Glycated Hemoglobin	4.4-14.2	5.83	>=5.6	56.30%	clinical
C-reactive protein	0.04-225.81	4.12	>=3.84	28.90%	empirical
DHEA	0.1-621.39 (female) 0.62-1714.53 (male)	70.13 (female) 69.47 (male)	<13 or >730 (female) <24 or >1640 (male)	12.9% (female) 24.8% (male)	clinical

the 75th percentile for C-reactive protein. Following Geronimus, et. al. (2006), we also gave those who were in the normal range but taking medications for blood pressure or diabetes a score of 1 for diastolic and systolic blood pressure or glycated hemoglobin, respectively (see Geronimus et al., 2006). This approach allows us to more accurately account for the effects of the social environment on risk, even if medication is used to control the biological response.

The scores from these biomarkers were summed to a single allostatic load score with a range of 0 (low allostatic load) to 6 (high allostatic load). Table 1 provides the clinical cut-offs used and weighted percent of the sample falling outside of the normal range for each marker.

Perceived Stress. Perceived stress was measured using four-items of Cohen's Perceived Stress Scale used collected in the NSHAP study (Cohen, Kamarck, & Mermelstein, 1983; Williams et al., 2009). These items were scored used a Likert-type scale of rarely (0), some of

the time (1), occasionally (2) or most of the time (3). Items were reversed where necessary so that higher scores were indicative of higher levels of perceived stress and summed to create a single scale (range 0-12).

Subjective Social Status. We measured subjective social status based on two questions about the participant's perceived social status: How financially well off they were compared to 1.) friends, family, neighbors and other people they know; and 2.) other Americans broadly. Answers were provided using a Likert-type scale of far below average (-2), below average (-1), average (0), above average (1) and far above average (2). Scores were summed and centered (range -4-4).

Education. Self-reported education is modeled as a continuous covariate of years of education (range 0-16).

Income and Assets. We used measures for Wave II total household income and assets. Income is a continuous measure of total household income in the prior year ($0-$1 million), and assets is a continuous measure of total household wealth, including real estate, pensions and other investments ($0-$9.9 million).

Covariates. All of our models controlled for gender and age at Wave III.

Analysis

We calculated Pearson's correlation coefficient and Spearman's rho for continuous and categorical variables, as appropriate. We also calculated weighted means and standard deviations or weighted percentages by race for all variables used in our analyses. We then tested for social gradients in education, income and assets for cognitive function and cognitive decline for the population as a whole, and by race using standard regression procedures. We also examined if

the effect of our markers of weathering and status anxiety on cognition were moderated by race or gender or were mediators in the race-cognition relationship. Finally, we modeled moderated mediation (conditional process analysis) for those variables for which we found both moderated and mediated effects in the preliminary models. All mediation, moderation and conditional process models were constructed using structural equation analysis with manifest variables standardized as z-scores, following the procedures described by Hayes (Hayes, 2017). Model fit was evaluated using root mean square error of approximation (RMSEA <0.06), comparative fit index (CFI>0.95) and standardized root mean square residual (SRMR<0.05) (L. T. Hu & Bentler, 1999). Standard errors and bias-corrected confidence intervals for final models were calculated using a bootstrapping approach with 2,000 replications.

Missing values. We used a two-step approach to accounting for missing data on our independent variables. When available, Wave II values were used as the primary response for all independent variables. If values were missing in Wave II, they were replaced with those from Wave I, as available. Allostatic load was calculated exclusively from Wave II data, as this was the only time point that collected all of these measures. For education, only 2 individuals were missing values on the continuous variable. However, both had available categorical education responses as “less than high school.” These 2 observations were given a value of 11 in the continuous education variable.

Remaining missingness was assumed to be Missing at Random. Values were imputed using a bootstrapping approach and maximum likelihood estimator. All analyses were conducted using Stata 14 (StataCorp, College Station, TX).

Results

Sample. The combined sample from all three waves of data (not accounting for attrition) was 6,489. Of these, 4,118 did not have valid responses to the CCFM (cognition) screening in both Waves II and Waves III, 319 were not classified as AA or NHW, and 526 were missing on one or more independent variable. We had a non-imputed sample of 1,526 (NHW=1,308; AA=218) and an imputed sample of 2,052 (NHW=1,709; AA=343).

Descriptive Statistics. Table 2 provides a correlation matrix for the non-imputed sample (n=1,526). The strongest correlations are between cognition at time 1 and time 2, and cognition at both time points with education, age, race and subjective social status. Additionally, income, assets, subjective social status and education were significantly correlated between ±0.22-0.44. Interestingly, we observed no correlation between our measures of stress, allostatic load and perceived stress (0.01; $p>.05$). Allostatic load was lowly correlated with any other variable; the strongest significant correlation was with race at 0.16. Perceived stress was moderately correlated with cognition at both time points, education, subjective social status and race, with significant correlations ranging ± 0.1-0.22.

We also observed significant variation bivariate associations of the variables by race. Compared to NHWs, AAs had lower cognitive function scores at both time points ($p<0.001$), fewer years of education ($p=0.04$), lower assets and income ($p<0.001$), lower subjective social status ($p=0.008$) and higher allostatic load ($p<0.001$) and perceived stress ($p=0.007$). Table 2 displays all results from bivariate associations for the non-imputed sample.

TABLE 11. *Correlation matrix of exogenous and endogenous variables.*

	1	2	3[+]	4[+]	5	6	7	8	9	10
1. Cognition T2	1.00									
2. Cognition T1	0.68*	1.00								
3. Race[+]	-0.29*	-0.32*	1.00							
4. Gender[+]	0.07*	0.10*	0.07*	1.00						
5. Age	-0.38*	-0.28*	0.00	-0.05*	1.00					
6. Education	0.39*	0.44*	-0.18*	-0.08*	-0.13*	1.00				
7. Income	0.18*	0.19*	-0.21*	-0.19*	-0.17*	0.29*	1.00			
8. Assets	0.14*	0.12*	-0.32*	-0.15*	0.00	0.22*	0.41*	1.00		
9. Subjective social status	0.22*	0.26*	-0.17*	-0.11*	-0.11*	0.40*	0.43*	0.36*	1.00	
10. Perceived stress	-0.20*	-0.18*	0.10*	0.07*	0.03	-0.19*	-0.08*	-0.09*	-0.22*	1.00
11. Allostatic load	-0.11*	-0.10*	0.16*	-0.07	0.00	-0.09*	-0.07*	-0.11*	-0.11*	0.01

[+]Spearman's rho, all others calculated with Pearson's correlation coefficient; *p<0.05

Mediation, moderation and conditional process analysis

We analyzed mediation, moderation and conditional process models with and without multiple imputation, finding comparable values. We therefore report only the findings from our imputed models. We observed a social gradient in both race groups for the relationship between education and cognitive function only, but not for the relationships between household income and assets with cognitive function. We tested for moderation by race and gender for all of our hypothesized mediators. We observed one statistically significant moderated effect by race in allostatic load on cognitive decline. However, when testing for this conditional indirect effect in our mediation model, it was no longer significant, and the interaction term was removed from our final models. None of the effects in our models were moderated by gender. Figures 4-8 below show the mediated effects of education and markers of status anxiety and weathering in the load in the relationship between race and cognition at Wave II (time 1) and Wave III (time 2)

TABLE 12. *Demographic characteristics of included NSHAP participants.*

	Non-Hispanic White, weighted % or mean (sd)	**African American, weighted % or mean (sd)**	**Adjusted Wald p-value**
Cognition Time 2 (0-20)	15.13 (3.20)	11.91 (5.08)	<0.001
Cognition Time 1 (0-20)	15.70 (2.76)	12.45 (4.95)	<0.001
Age (43-95)	74.89 (6.84)	74.20 (8.86)	0.21
Male	46.9%	42.5%	0.51
Female	53.1%	57.5%	
Years of Education (0-16)	13.39 (2.06)	12.62 (3.38)	0.04
Total Household Assets ($0-$9,999,999)	$760,012 ($1.5 mill)*	$215,338 ($509,217)	<0.001
Total Household Income ($0-$1,000,000)	$68,979 ($84,327)	$45,096 (52,343)	<0.001
Allostatic Load (0-6)	1.96 (1.22)	2.58 (1.57)	<0.001
Perceived Stress (0-12)	2.73 (2.44)	3.24 (3.43)	0.007
Subjective Social Status (-4-4)	-0.16 (1.57)	-0.75 (2.46)	0.008

***$**1,504,143

in the National Social Life Health and Aging Project cohort. Dashed lines indicated tested, but non-significant paths. Solid lines indicate significant paths at $p<0.05$.

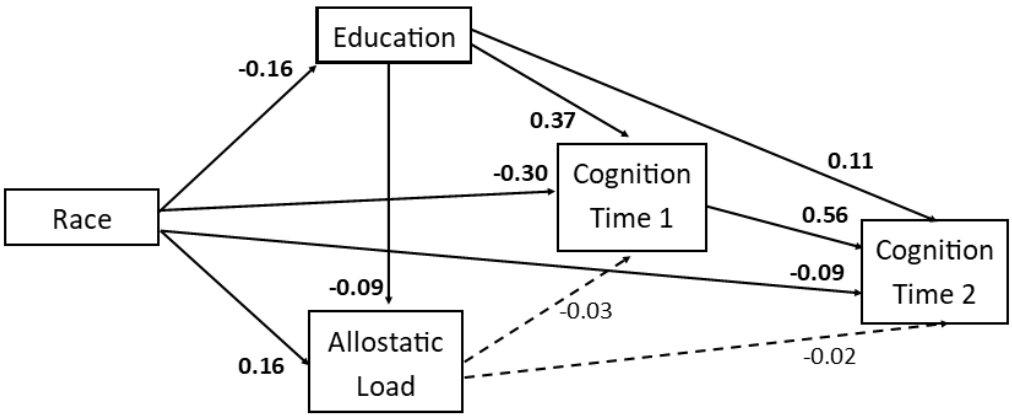

FIGURE 4. *Mediated path analysis for the effects of education and allostatic load.*

Allostatic load. In our mediation model, the relationships were comparable between race and education (-0.16; 95% CI: -0.23, -.10) and allostatic load (0.16; 95% CI: 0.11, .22), indicating that AAs had lower levels of education and higher allostatic load scores than NHWs (Figure 4). However, only education was a mediator of the race-cognition relationship at either time point. Additionally, while education and allostatic load had a weak negative association (-0.09; 95% CI: -0.14, -0.04), allostatic load did not mediate the relationship between education and cognition at either time point. Regardless, the relationship between race on cognition remained strong, even after accounting for education and allostatic load.

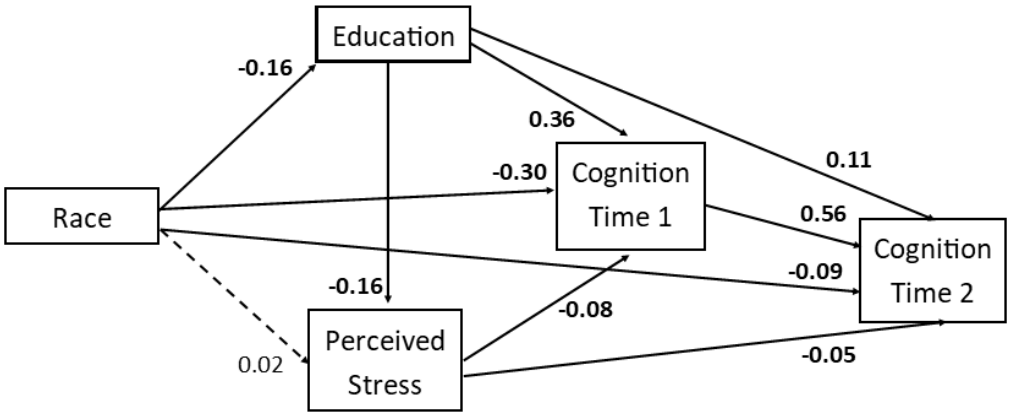

FIGURE 5. *Mediated path analysis for the effects of education and perceived stress.*

Perceived Stress. Perceived stress is a small, but significant, mediator of the relationship between education and cognition, but is not a mediator of the race-cognition relationship (Figure 5). As observed for allostatic load, the total effect for race and cognition in the presence of perceived stress continues to be substantial even after controlling for education.

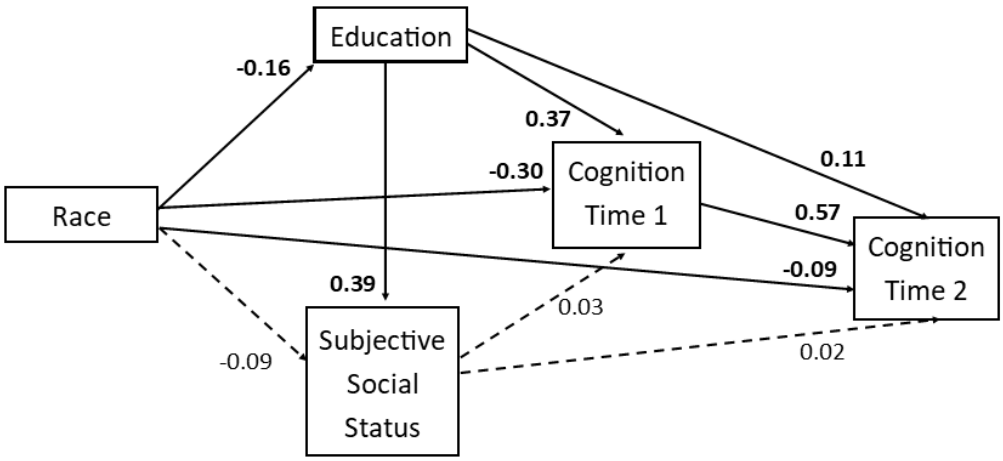

FIGURE 6. *Mediated path analysis for the effects of education and subjective social status.*

Subjective Social Status. Although education was strongly and significantly associated with subjective social status (0.39; 95% CI: 0.3, 0.45), subjective social status is not a mediator of the race-cognition or the education-cognition relationships (Figure 6).

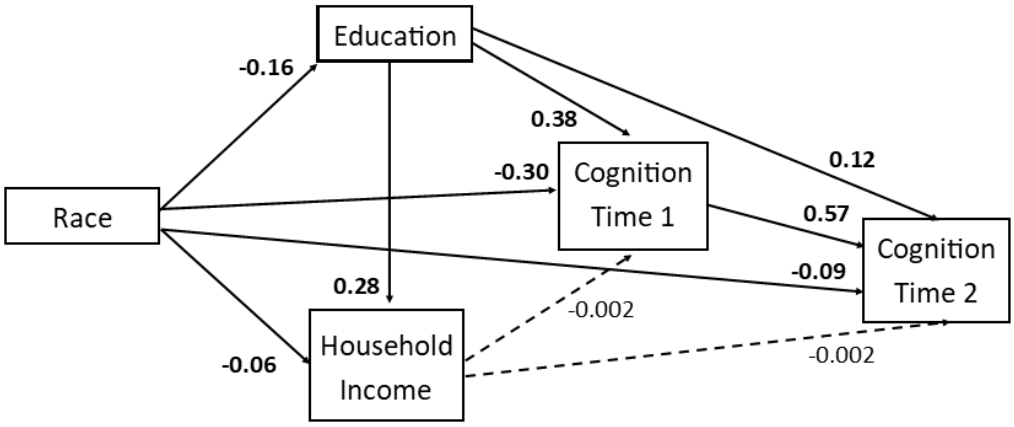

FIGURE 7. *Mediated path analysis for the effects of education and household income.*

Household Income. Race is associated with household income both directly and indirectly through the effects of education (Figure 7). However, neither of these pathways contribute to cognitive outcomes.

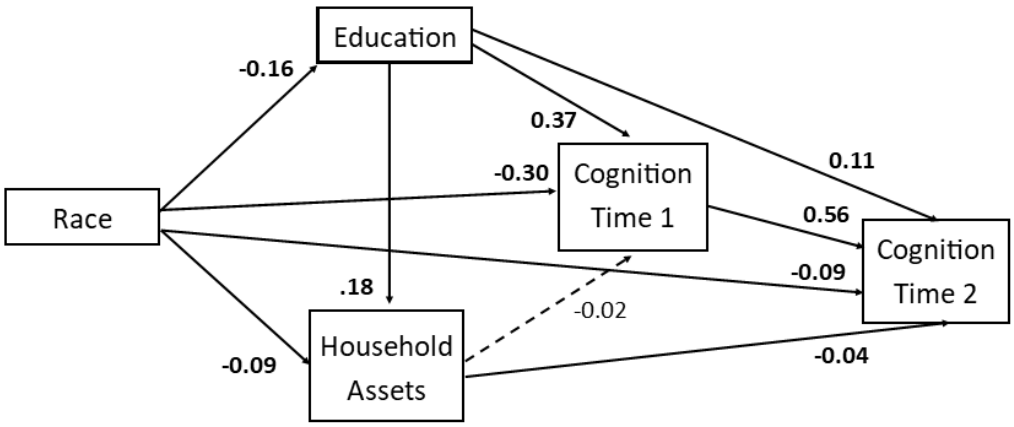

FIGURE 8. *Mediated path analysis for the effects of education and household assets.*

Household Assets. Household assets has a small but significant mediational effect on the relationships between race and cognition at time 2, and race on cognition at time 2 when mediated by education (Figure 8).

Discussion

Our models tested for the effects of weathering and status anxiety in explaining racial disparities in Alzheimer's disease risk (Geronimus et al., 2006; Marmot, 2004). Education was consistently observed to be an important mediator in the race-cognition relationship. We also observed that perceived stress and household assets were statistically significant mediators of the relationships between race, education and cognition. Allostatic load, subjective social status and household income did not mediate the relationships between race and cognition, or education and cognition. The significant but small mediated effects for perceived stress and household assets, and the robustness of the direct effects of race in these models suggest that other unmeasured factors are critical to understanding racial differences in Alzheimer's disease risk.

Few studies have empirically tested for markers of status anxiety or weathering as explanatory mechanisms for racial disparities in AD in population-based cohorts. To date, none to our knowledge have looked explicitly at allostatic load. One study has examined the inflammatory marker C-reactive protein, and found that this marker mediated the relationship between self-reported discrimination and baseline episodic memory, but not with change in memory over time (Zahodne, Kraal, Sharifian, Zaheed, & Sol, 2019). This finding is in contrast to our model of allostatic load, a measure that included C-reactive protein. This discrepancy may be due to the different sensitivity of C-reactive protein for global cognition (the outcome of this study) versus the more narrowly defined episodic memory (Bettcher et al., 2012).

Other studies that have examined perceived stress found that it was associated with lower baseline cognition (Aggarwal et al., 2014) and faster rate of cognitive decline in both AAs and NHWs, which could be consistent with our finding of a mediated effect through perceived stress (Aggarwal et al., 2014; Turner, James, Capuano, Aggarwal, & Barnes, 2017). Another study found that higher rates of perceived discrimination among AAs was a substantial contributor to racial disparities in memory function (Zahodne, Sol, & Kraal, 2019). While these studies controlled for education, they did not examine if and how these alternate mechanisms might shift the understanding of how education operates on AD disparities through direct and indirect pathways. By doing so in this analysis, we contribute to this body of literature by further substantiating that the effect of education on cognition is persistently stronger than alternate socioeconomic and stress pathways, which points to the importance of cognitive stimulation and early life neuro-development, as suggested by the cognitive reserve hypothesis. The explanation for understanding population-level disparities in AD risk is reinforced by a recent finding that

cohort differences in cognitive function and cognitive trajectories can be attributed to differences in educational attainment (Leggett et al., 2019).

Limitations

While our study examined a composite of markers indicative of biological response to stress, we were limited to six available biomarkers for the cardiovascular, metabolic and inflammatory systems. Other studies examining allostatic load have included up to 17 biomarkers in this index, increasing the explanatory potential and sensitivity of this measure (Juster et al., 2010). A second limitation was that we did not examine positive response to stress via coping or resilience processes in this study, which may have contributed to some of the non-significant findings in our models. Observational studies have shown a decrease in health disparities with age that may reflect a selective survival bias in that only those individuals with social and biological resilience live into older ages (Crimmins, Hayward, & Seeman, 2004; J. Kim & Miech, 2009). It is possible that our sample, with a mean age of 74, will have selectively higher levels of resilience that were not accounted for by this study's measures.

Conclusions

Our findings uphold the cognitive reserve hypothesis that education partially explains racial disparities in Alzheimer's disease risk. Although markers for weathering or status anxiety were not significant in our models does not minimize the importance of social equity for health outcomes. Processes of discrimination that continue to systematically reduce access to quality education among AAs will continue to contribute to racial disparities in AD risk. Additionally, the divergent findings from comparable studies point to the need for a deeper examination of these hypotheses in alternative populations with alternative indicators. Cross-national

comparisons with other countries that have legacies of discrimination, such as South Africa, could help researchers to home in on the precise processes of interaction between social experiences and biological outcomes, and contributors to resilience that may be impacted through policies to mitigate their cognitive impact.

CHAPTER 5: CONCLUSIONS

The examination of racial and socioeconomic disparities in Alzheimer's disease (AD) risk has critical implications for public health practice and health disparities theory. Incidence of AD is steadily increasing as the population ages, and no therapeutic interventions are currently available to cure or effectively treat this progressive neurogenerative disease. The only available intervention is to minimize the risk from modifiable factors. At a basic level, this makes AD risk reduction simple and universal: eat nutritious food, engage in regular physical activity, stay socially and cognitively engaged, and manage existing chronic conditions (Livingston et al., 2017). However, the simplicity of these messages begins to break down in the face of racial and socioeconomic disparities. Disparities are by definition population-based. Addressing them requires a broader understanding of the structural factors that are operating above and beyond what can be accounted for by individual actions to minimize individual risk factors. The studies in this dissertation aimed to contribute to this effort by examining the most plausible mechanisms that connect social factors to individual AD risk. Cumulative Advantage/Disadvantage (CAD) theory provided an important theoretical framework to undertake this work, as it explicitly recognizes the interaction between social forces and individual circumstances across the life course (Dannefer, 2018). Status anxiety and weathering – two dominant health disparities theories – provided the theoretical rationale for potential mechanisms and offered a contrasting perspective from the cognitive reserve hypothesis that dominates in the AD literature.

The role of education in AD disparities

One of the weaknesses of the cognitive reserve hypothesis is that it relies on a tautological fallacy: The proxies of cognitive reserve – education, literacy, IQ – are also presumed to be the

causes of cognitive reserve. The studies presented in chapters 3 and 4 aimed to examine and overcome this tautology, with mixed findings. In looking for evidence of a social gradient in health, chapter three demonstrated that those who completed high school and college were associated with better self-reported cognitive decline than those who started college, but did not complete a degree (Peterson, Carvajal, McGuire, Fain, & Bell, 2019). This finding is in contrast to that proposed by the cognitive stimulation mechanism that is assumed in the cognitive reserve hypothesis. If cognitive reserve were the sole mechanism of the education-cognition relationship, any additional years of education should be associated with better health. Rather, the finding in chapter 3 suggests that cognitive changes may be influenced by social status – providing some initial support for the status anxiety hypothesis.

Chapter 4 expanded upon this idea by examining the direct and indirect effects of education on AD risk. In doing so, the study juxtaposed the interpretation of education as a proxy for cognitive reserve against the interpretation that education is a proxy of social status. While the direct effect indicative of cognitive reserve remained constant in all models, my findings show some evidence of the social status effect on racial disparities in AD, as household assets late in life partially mediate the education-cognition and the race-cognition relationship. This further substantiates the potential contribution of social status as a "fundamental cause" of AD disparities (Phelan et al., 2010).

Inequality and discrimination in AD disparities

It is important to note that authors of prior studies on racial disparities in AD have pointed to discrimination and the role of Jim Crow-era educational segregation as a critical social force shaping the disparity in AD risk (see Sachs-Ericsson & Blazer, 2005; Sisco et al., 2015).

However, these researchers continued to assume that the effect of education operated via cognitive stimulation in their empirical analysis, rather than considering how ongoing experiences with inequality (extending the status anxiety hypothesis) and social discrimination (via the weathering hypothesis) may contribute to their findings.

I aimed to fill this gap in chapter four by examining the potential roles of status anxiety and weathering in contrast to that of education. Both status anxiety and weathering assume a psychosocial response to social structure that contributes to worse health via chronic stress. Interestingly, for the racial disparities examined in chapter 4, perceived stress was a significant partial mediator of racial disparities in cognition, and of education's effects on cognition, though the biological measure of chronic stress (allostatic load) was not. However, I did not observe a parallel process for socioeconomic disparities in chapter three, as state-level income inequality did not have a significant effect on self-reported cognitive decline.

Implications for public health policy and practice

Although more empirical evidence is needed, these studies provide important considerations for public health policy and practice. First, they confirm the importance of education for AD risk – regardless of the operating mechanism. Disparities continue to persist in educational attainment and quality by race and socioeconomic status (Ryan & Bauman, 2016). Disinvestment in public education systems from pre-kindergarten through university presents a serious threat to the racial equity and class mobility, which in turn impacts the health outcomes of future generations. This recognition makes equitable access to quality education an important domain for public health action. Additionally, policies that counteract structural and implicit forms of discrimination in other domains, such as housing (Rugh & Massey, 2014) and health

care (Lutfey & Freese, 2005), may also contribute to reducing disparities in AD risk. Finally, these studies demonstrate the need to think about how to intervene on a multitude of factors across the life course – and not just within an early life "critical period." While promotion of a healthy lifestyle is always prudent, interventions that also promote positive social and cognitive engagement and help to reduce chronic stress in mid- and late-life may also help to buffer some of the negative health effects of accumulated disadvantage.

Future research

Future studies should continue to examine the theories tested here for consistency of findings in different sample populations. Cross-national comparisons that provide differing contexts of inequality and discrimination could provide insights into how and when the factors associated with cumulative advantage/disadvantage contribute to AD risk. It is also pertinent to examine various cognitive outcomes, including AD incidence, in future studies. Due to limitations in the data used in the studies presented here, the findings presented in this dissertation are based on self-reported cognitive decline and one cognitive assessment, and therefore may lack the sensitivity or robustness of findings from studies of incident AD. Additional studies that confirm and expand upon the findings here will provide a more substantial evidence base from which we can enact important policy interventions that correct the processes of cumulative disadvantage that act as a fundamental cause of AD disparities. If additional studies do not find evidence for status anxiety or weathering effects of cumulative disadvantage, AD may serve as an important counterfactual case to increase understanding of when and how processes of inequality and discrimination get under the skin or into the brain to shape health disparities.

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APPENDIX A: MANUSCRIPT 1

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The role of social and behavioral risk factors in explaining racial disparities in age-related cognitive impairment: a structured narrative review

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ABSTRACT

Alzheimer's disease (AD) is a growing public health concern with large disparities in incidence and prevalence between African Americans (AAs) and non-Hispanic whites (NHWs). The aim of this review was to examine the evidence of association between six modifiable risk factors (education, smoking, physical inactivity, obesity, social isolation, and psychosocial stress) and Alzheimer's disease risk in AAs and NHWs. We identified 3,437 studies; 45 met inclusion criteria and were included in this review. Of the examined risks, education provided the strongest evidence of association with cognitive outcomes in AAs and NHWs. This factor may operate directly on Alzheimer's disease risk through the neurocognitive benefits of cognitive stimulation or indirectly through social status.

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Alzheimer's disease; African American; cognitive decline; disparities; education

Background

Significant racial disparities have been observed in Alzheimer's disease and related dementias. A recent review of prevalence and incidence studies across racial/ethnic populations found that African Americans (AAs) have consistently higher rates of Alzheimer's disease and related dementias when compared with non-Hispanic Whites (NHWs) (Mehta & Yeo, 2016). Alzheimer's disease, the most common form of dementia, results in declines in cognitive and physical functioning that, over time, increase the need for personal care in activities of daily living. With inadequate availability of long-term care services, many families of individuals living with dementia reduce their paid employment to take on roles of caregiving, with broader consequences for their own health (Alzheimer's Association, 2018; Richardson, Lee, Berg-Weger, & Grossberg, 2013). As the number of individuals diagnosed with Alzheimer's disease continues to increase, so will its impacts to families and society, and the disparities between AAs and NHWs may widen if the risks driving them are not better understood and effectively addressed (Hebert, Weuve, Scherr, & Evans, 2013).

Racial disparities have been observed across a wide array of health conditions, with a complex network of factors likely contributing. The National Institutes on Aging Health Disparities Research Framework points to factors across environmental, socio-cultural, behavioral and biological levels of analysis that should be explored to

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understand health disparities (Hill, Pérez-Stable, Anderson, & Bernard, 2015). While biological factors, such as genetic risk, set the stage for Alzheimer's disease risk, it is the exposure and accumulation of environmental, sociocultural and/or behavioral factors over time that shapes the vulnerability to biological risk and likely produces the disparate rates of Alzheimer's disease among AAs (McDonough & Allen, 2018). It is therefore critical to distinguish between biological *differences* in risk and the embodiment of social factors, including discrimination, that drives racial health *disparities* (Gravlee, 2009; Krieger, 2000). It is important to understand how modifiable environmental, sociocultural and behavioral mechanisms that shape AD risk may contribute to racial disparities.

The Lancet Commission on Dementia Prevention, Intervention, and Care has identified nine modifiable risk factors that account for 35% of population attributable risk of dementia: education, mid-life hypertension, mid-life obesity, mid-life hearing loss, smoking, physical activity, depression, diabetes and social isolation (Livingston et al., 2017). Much of what is known about Alzheimer's disease risk is rooted in research that tends to underrepresent AAs and other minorities, limiting knowledge of if the distribution of effect of known risk factors varies by race/ethnic group. Such gaps have been identified for biological risks of Alzheimer's disease, and may similarly be a major concern for the potentially modifiable factors (Haga, 2010). Indeed, the Lancet review focused on studies largely published on populations in Europe and the United States, and did not explore possible racial variation in risk (Livingston et al., 2017). Of the risks identified in the Lancet report, AAs have higher prevalence rates of some factors, including diabetes, hypertension, physical inactivity, and low education, though not all (Keadle, McKinnon, Graubard, & Troiano, 2016; Menke, Casagrande, Geiss, & Cowie, 2015; Nwankwo, Yoon, Burt, & Gu, 2013; United States Census Bureau, 2016). As there is currently no effective treatment for Alzheimer's disease, our best approach for reducing racial disparities is in understanding if and how modifiable risks vary by race, and developing interventions that target these factors.

The aim of this review is to compile and evaluate if the evidence for known social and behavioral modifiable risk factors for Alzheimer's disease helps to explain the observed disparities between AAs and NHWs. While the Lancet report identified nine modifiable risk factors, we chose to focus this review on five: education, smoking, physical inactivity, social isolation, and obesity. We selected these as priority modifiable risk factors for racial disparities because they are 1) most likely to precede others in a chain of risk (e.g., low education is associated with physical inactivity, which can contribute to obesity, which is a risk for hypertension, which is a risk for Alzheimer's disease); and 2) are plausibly responsive to intervention (including policy change), and therefore amenable to risk reduction in Alzheimer's disease. Although not highlighted by the Lancet review, we also included psychosocial stress as a social risk for Alzheimer's disease in the review, given the growing evidence it is a key mechanism for the social environment to "get under the skin" and drive health disparities in a broad range of health outcomes (Geronimus, 1992; Geronimus, Hicken, Keene, & Bound, 2006; McEwen, 2012). Our findings are expected to provide direction for intervention and risk reduction of Alzheimer's disease in African American populations and identify gaps for future research.

Methods

We conducted a structured narrative review that combined a systematic, documented search strategy with supplemental searches and citation review to ensure our search was both comprehensive and targeted to our research aim. While systematic reviews are considered the gold standard for synthesizing the state of evidence in areas where there is a rich source of empirical studies and where elements of study design strength can be assessed, we determined that a narrative review more appropriately fits the goal of this project (Higgins & Green, 2011). Consequently, our approach allowed us to include studies of diverse methods and aims that provided pertinent evidence for our research aim. At the same time, we sought to overcome a subjectivity bias in the selection of included articles through the systematic structured search component and to provide documentation that would allow for replication, addressing two common critiques of narrative reviews (Ferrari, 2015).

Search strategy

We used a three-step search strategy that included a systematic literature search, exploratory searches, and citation review. The systematic search was conducted in June 2018. We searched Pubmed, Embase, Psychinfo and Sociological Abstracts using MeSH (or equivalent) terms for peer-reviewed, English language papers. We conducted additional expansive keyword searches for each of the risk factors in the aforementioned databases from June 2018 to July 2018. Finally, we reviewed the citations of the included studies for additions that met our inclusion/exclusion criteria.[1] Comparable searches were completed for each of the risk factors in all four databases.

Inclusion and exclusion criteria

We used a standardized rubric with pre-specified criteria to identify studies for inclusion (see Appendix). A study was included if it: 1) analyzed as a primary outcome cognitive function at a single point in time, rate of cognitive change over time, and/or Alzheimer's disease incidence. Although our primary interest is in explaining racial differences in Alzheimer's disease, we found it important to include studies that looked at both cross-sectional cognitive function and rate of cognitive decline over time, as these studies provide larger population estimates that are indicative of Alzheimer's disease risk before the onset of disease. While not all individuals who have a low cognitive function score or cognitive decline will progress to Alzheimer's disease, inclusion of these studies substantially increases the studies that meet inclusion criteria, and helps to minimize bias from looking only at those populations who have been willing and able to seek medical services that resulted in an Alzheimer's disease diagnosis.

We also focused exclusively on studies that 2) quantitatively tested for differences in AAs and NHWs 3) in the effect of one or more of the six social and behavioral modifiable risk factors that are the focus of this review, and were 4) cohort or cross-sectional observational studies of 5) community-dwelling mid-life and older adults who did not have another health issue that might impact their cognition (e.g., history of lupus). We did not specifically set age parameters on included studies, though because of the focus

on Alzheimer's disease almost all study participants were ages 45 and older. However, we recognize that many individuals living with Alzheimer's disease have mixed dementia that includes vascular dementia, which is strongly associated with a history of stroke (Schneider, Arvanitakis, Bang, & Bennett, 2007).

Analysis

For each included study, we compiled findings on the associations between the risk factor and cognitive outcomes (cognitive function as a single time point, rate of cognitive decline and incidence Alzheimer's disease), and if these relationships varied by race. We summarized this evidence by risk factor and classified our findings as strong, moderate or weak/inconclusive for explaining racial disparities in Alzheimer's disease risk. We considered the evidence to be strong if the findings for the relationship between the risk factor and race for each of the cognitive outcomes were consistent across studies, moderate if findings across studies were consistent for at least one of the cognitive outcomes but inconsistent or unavailable for the other cognitive outcomes, and weak/inconclusive if findings were inconsistent across one or more of the cognitive outcomes.

Results

Included studies

The structured searches yielded 3,298 non-duplicated articles. Of these, 36 were included in a full-text review, and 18 met our criteria for inclusion in our analysis. Through keyword supplemental searches, we identified an additional 23 studies that met our criteria and through citation review, we identified an additional 4 studies. Figure 1 provides the CONSORT flow diagram for our search and limitation process. Table 1 provides the complete list of included studies and the evaluated risk factors for each.

Cognitive function, cognitive decline, and Alzheimer's disease incidence

Of the included studies, 30 examined effects on cognitive function at a single point in time, 26 examined effects on cognitive decline over time, and 6 examined effects on incident Alzheimer's disease or non-differentiated dementia. Ten out of 30 studies that included cognitive function as an outcome reported racial comparisons of baseline cognitive function unadjusted for the risk factor(s) of interest (Barnes et al., 2011, 2005; Carvalho et al., 2015; Crowe, Clay, Sawyer, Crowther, & Allman, 2008; Kuczmarski, Cotugna, Mason, Evans, & Zonderman, 2015; Liu, Glymour, Zahodne, Weiss, & Manly, 2015; Masel, Raji, & Peek, 2010; Sachs-Ericsson & Blazer, 2005; Sheffler, Moxley, & Sachs-Ericsson, 2014; Vásquez, Botoseneanu, Bennett, & Shaw, 2015). Of these, all observed that AAs had a lower cognitive function for most or all of the domains examined. Two of the six studies with incident dementia as an outcome reported unadjusted dementia incidence by race. One found that AAs had a higher risk of dementia (Garcia, Saenz, Downer, & Wong, 2018), while the second found that unadjusted risk was equal for

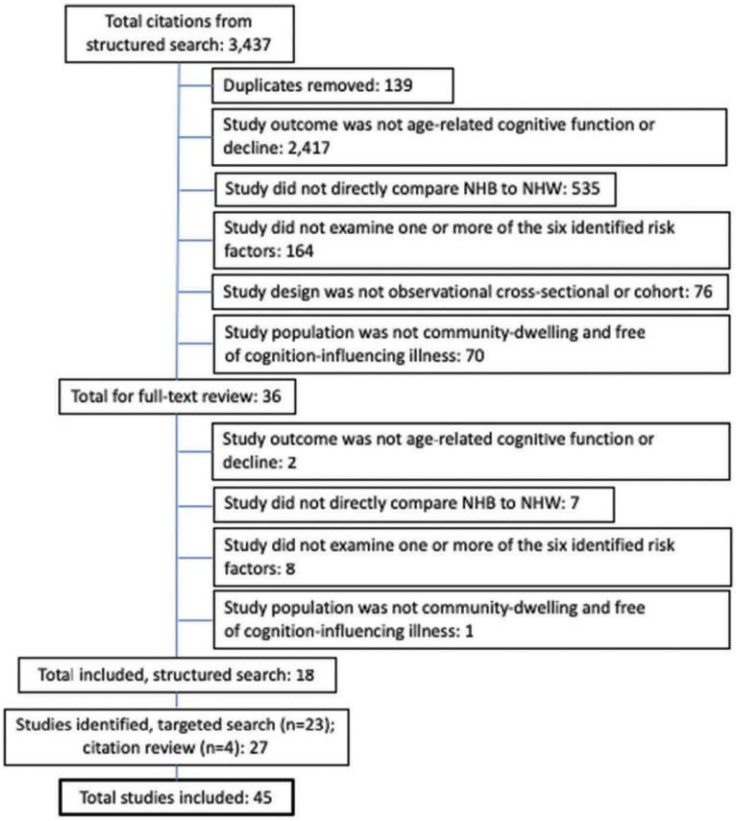

Figure 1. Flow diagram of structured and unstructured study inclusion and exclusion process.

NHWs and AAs (Rodriguez, Aranda, Lloyd, & Vega, 2018). No studies reported unadjusted comparisons of cognitive decline by race.

Study cohorts and geographic dispersion

Twenty cohorts or locally recruited populations were analyzed in the 45 included studies. The most frequently used cohorts were the Chicago Health and Retirement Project (n = 9) and the nationally representative Health and Retirement Study (n = 7). Most of the research studies included in this analysis relied on populations residing in the Northeast or Southeast regions of the United States. This pattern is logical as these regions tend to have higher densities of AAs than other parts of the US, though it limits the generalizability of findings.[2]

We report the remainder of our findings by risk factor from those with the most to least identified studies. Studies that examined more than one of the risk factors of interest are discussed in all relevant sections. We also discuss patterns in findings in each

Table 1. Included studies by risk factor(s) and cognitive outcome(s) examined.

Citation	Participants	Data source	Outcome(s)	Risk factor(s)
Arpawong et al., 2016	AA (n = 1,558); NHW (n = 9,351); Hispanic (n = 1,079)	Health and Retirement Study	Cognitive decline	Education
Barnes et al., 2005	AA (n = 125); non-AA (n = 327)	Patients of Rush Alzheimer's Disease Center, and Chicago-area adult day centers	Cognitive decline	Education
Barnes et al., 2011	AA (n = 6,083); NHW (n = 3,541)	Chicago Health and Aging Project	Cognitive function	Education
Garcia et al., 2018	AA (n = 3,715); NHW (n = 12,762) US-born Hisp. (n = 992); Foreign-born Hisp. (n = 1,630)	Health and Retirement Study	Cognitive Impairment and dementia incidence	Education
Wilson et al., 2009	AA (n = 4377); NHW (n = 2156)	Chicago Health and Aging Project	Cognitive decline	Education
Rodriguez et al., 2018	**Low education**: AA (n = 121); NHW (n = 215); Hispanic (n = 71) **High education**: NHW (n = 375); non-NHW (n = 37)	ADAMS HRS	Dementia incidence	Education
Crowe et al., 2013	AA (n = 223) NHW (n = 210)	University of Alabama-Birmingham Study of Aging	Cognitive function and decline	Education quality
Liu et al., 2015	**HRS**: AA (n = 2,362) NHW (n = 13,313) **WHICAP**: AA (n = 1,013) NHW (n = 540)	Health and Retirement Study; Washington Heights-Inwood Columbia Aging Project	Cognitive function	Education quality
Sisco et al., 2015	Black (n = 1,192) White (n = 487) Note: Hispanic included in above categories	Washington Heights-Inwood Columbia Aging Project	Cognitive function	Education quality
Reuser et al., 2011	AA (n = 3,294) NHW (n = 17,342) Hispanic (n = 762)	RAND Health and Retirment Study	Cognitive function	Education obesity smoking
Masel et al., 2010	AA (n = 1,612) NHW (n = 6,723) Hispanic (n = 869)	Health and Retirement Study	Cognitive function	Education physical activity
Vásquez, et. al., 2015	AA (n = 548) NHW (n = 2,652) Hispanic (n = 224)	Health and Retirement Study	Cognitive function and decline	Education physical activity smoking
Carvalho et al., 2015	AA (n = 118); NHW (n = 461)	Memory Health and Aging study	Cognitive function and decline	Education/literacy

(*Continued*)

Table 1. (Continued).

Citation	Participants	Data source	Outcome(s)	Risk factor(s)
Chin et al., 2012	AA (n = 51) NHW (n = 193)	University of Pennsylvania Alzheimer's Disease Center patients	Cognitive function	Education/literacy
Crowe et al., 2008	AA (n = 299); NHW (n = 311)	University of Alabama-Birmingham Study of Aging	Cognitive function	Education/literacy
Dotson et al., 2009	AA (n = 757); NHW (n = 588)	Healthy Aging in Neighborhoods of Diversity across the Life Span	Cognitive function	Education/literacy
Kaup et al., 2014	AA (n = 932); NHW (n = 1526)	Health Aging and Body Composition	Dementia incidence	Education/literacy
Manly et al., 2002	AA (n = 192); NHW (n = 192)	Washington Heights-Inwood Community Aging Project	Cognitive function	Education/literacy
Sachs-Ericsson & Blazer, 2005	AA (n = 1,690); NHW (n = 1,407)	Duke Established Populations for Epidemiologic Studies of the Elderly	Cognitive decline	Education/literacy
Yaffe et al., 2009	AA (n = 897) NHW (n = 1612)	Health Aging and Body Composition Study	Cognitive resilience (absence of cognitive decline)	Education/literacy isolation obesity physical activity smoking
Kaup et al., 2015	AA (n = 329) NHW (n = 341)	Health Aging and Body Composition Study	Cognitive resilience (absence of cognitive decline)	Education/literacy isolation obesity physical activity smoking
Kuczmarski et al., 2015	AA (n = 972) NHW (n = 772)	Healthy Aging in Neighborhoods of Diversity across the Life Span	Cognitive function	Education/literacy obesity
Barnes et al., 2004	AA (n = 2,421); NHW (n = 1,478)	Chicago Health and Aging Project	Cognitive decline	Isolation
Han et al., 2016	AA (n = 590); NHW (n = 590)	Rush Memory & Aging Project; Minority Aging Research Study	Cognitive function	Isolation
Kats et al., 2016	AA (n = 3,090); NHW (n = 10,029)	Atherosclerosis Risk in Communities Study	Cognitive function and decline	Isolation
Zahodne et al., 2017	AA (n = 225); NHW (n = 170); Hispanic (n = 153)	Washington Heights-Inwood Columbia Aging Project	Cognitive function	Isolation
Arvanitakis et al., 2018	AA (n = 704); NHW (n = 1,430)	Minority Aging Research Study; Rush Memory and Aging Project	Cognitive decline	Obesity
Bressler et al., 2013	AA (n = 2,083); NHW (n = 8,364)	Atherosclerosis Risk in Communities Study	Cognitive decline	Obesity
Bryant et al., 2014	AA (n = 546) NHW(n = 4,104 Hispanic (n = 110)	Health and Retirement Study (2010)	Cognitive function	Obesity
Gottesman et al., 2017	AA (n = 4,267) NHW (n = 11,477)	Atherosclerosis Risk in Communities Study	Dementia incidence	Obesity

(*Continued*)

Table 1. (Continued).

Citation	Participants	Data source	Outcome(s)	Risk factor(s)
Hu et al., 2012	AA (n = 25,042) NHW (n = 19,618)	Louisiana State University hospital-based longitudinal study	Dementia incidence	Obesity
Rajan et al., 2014	AA (n = 2,834) NHW (n = 1,221)	Chicago Health and Aging Project	Cognitive function and decline	Obesity
Sturman et al., 2008	AA (n = 2,371) non-AA (n = 1,514)	Chicago Health and Aging Project	Cognitive function and decline	Obesity
Rajan et al., 2015	AA (n = 4,976); NHW (n = 2766)	Chicago Health and Aging Project	Cognitive decline	Physical activity
Zhu et al., 2017	AA (n = 1,968); NHW (n = 4,484)	Reasons for Geographic and Racial Differences in Stroke project	Cognitive decline	Physical activity
Zhu et al., 2015	AA (n = 2,234); NHW (n = 4,864)	Reasons for Geographic and Racial Differences in Stroke project	Cognitive function	Physical activity
Aggarwal et al., 2014	AA (n = 4,081) NHW (n = 2,126)	Chicago Health and Aging Project	Cognitive function and decline	Psychosocial stress
Kaup et al., 2015	AA (n = 329) NHW (n = 341)	Health Aging and Body Composition	Cognitive resilience (absence of cognitive decline)	Psychosocial stress
Sheffler et al., 2014	AA (n = 2,235) NHW (n = 1,877)	Duke Established Populations for Epidemiologic Studies of the Elderly	Cognitive function	Psychosocial stress
Wilson, Barnes, et al., 2005	AA (n = 570) NHW (n = 575)	Chicago area residents age 65 and older.	Alzheimer's disease incidence	Psychosocial stress
Wilson, Bennett et al., 2005	AA (n = 2,723) NHW (n = 1,669)	Chicago Health and Aging Project	Cognitive function and decline	Psychosocial stress
Zuelsdorff et al., 2017	AA (n = 82) NHW (n = 1,232)	Wisconsin Registry for Alzheimer's disease Prevention (WRAP)	Cognitive function	Psychosocial stress
Aggarwal et al., 2006	AA (n = 530) Non-AA (n = 534)	Chicago Health and Aging Project	Alzheimer's disease incidence	Smoking
Bachman et al., 2003	AA (cases = 285; controls = 158) NHW (cases = 1,650; controls = 686)	Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study	Alzheimer's disease incidence	Smoking
Knopman et al., 2001	AA (n = 3,455) NHW (n = 10,593)	Atherosclerosis Risk in Communities Study	Cognitive function	Smoking

section separately for each of the three cognitive outcomes. Table 2 provides a summary of our findings.

1. Education

We identified 22 studies that examined education. Of these, 9 focused on years of education, 10 examined years of education in conjunction with literacy level, and 3 examined the quality of childhood education. We did not explicitly search for studies examining school quality or literacy level, but this subcategorization emerged upon review. As such, we are reporting our findings based on these subcategories of education to allow for a more detailed interpretation of possible mechanisms underscoring any observed associations.

Table 2. Summary of evidence and research gaps for each risk factor by cognitive measure.

Risk factor	Outcome of interest	State of evidence	Research gaps
Social isolation (n = 6)	Cognitive function (n = 3)	Isolation is associated with cognitive function, but there is no difference by race. It is inconclusive if social isolation is more prevalent in one race group.	Future research should examine prevalence in social isolation by race among older adults and explore if different measures of social isolation produce more consistent findings. Studies and data sets that connect social measures, including isolation, to incident AD are needed.
	Cognitive decline (n = 4)	Studies contradict if social support is more protective for NHW, or if there is no effect for either race group.	
	Incident AD or other dementia (n = 0)	NA	
Psychosocial stress (n = 6)	Cognitive function (n = 2)	Studies contradict if the negative effect of stress is stronger for AAs or NHWs. Moderate evidence suggests stress is more likely among AAs.	Studies relied on self-report measures of stress or stressful life events. Future studies should also examine the role of stress biomarkers. The finding for AD incidence is based on one study; future studies are needed to substantiate this evidence.
	Cognitive decline (n = 4)	Stress is associated with faster cognitive decline. Studies contradict if this effect is stronger in NHWs or AAs, or there is no difference by race.	
	Incident AD or other dementia (n = 1)	Stress is predictive of AD in NHWs but not AAs.	
Obesity (n = 10)	Cognitive function (n = 4)	Studies contradict if obesity is positively or negatively associated with cognitive function for AAs while having no effect in NHWs, or if there is no effect for either race.	The relationship between BMI and cognitive function is complex and follows a u-shaped curve. High mid-life BMI is a vascular risk factor while low and declining late-life BMI is an indicator of AD. Mean follow up times between BMI and cognitive testing in the included studies ranged from 0 to 23 years. Future research should aim to disentangle how the timing of obesity impacts AD risk.
	Cognitive decline (n = 4)	Findings contradict if there is an effect, and if the effect varies by race.	
	Incident AD or other dementia (n = 2)	Studies contradict if obesity is a risk or protective factor for AD, and if this varies by race.	
Physical activity (n = 7)	Cognitive function (n = 3)	Evidence suggests that physical activity is protective. The protective effect may be stronger for AAs, and partially attenuate racial disparities.	Because effects were predominately observed for cognitive function, future research should explore the association between physical activity throughout middle and late adulthood and incident AD.
	Cognitive decline (n = 5)	Studies are contradicted on if physical activity is protective for only NHWs, for both race groups, or has no effect in either race group.	
	Incident AD or other dementia (n = 0)	NA	
Smoking (n = 8)	Cognitive function (n = 5)	Studies are contradicted on if smoking has an effect. Those showing an effect did not observe a difference by race. One study found smoking may partially attenuate racial disparities.	Future research should look at possible third causes that would better connect smoking with racial disparities in AD. Reference group varied by study.
	Cognitive decline (n = 4)	Studies are contradicted on if smoking has an effect. None observed a difference by race.	
	Incident AD or other dementia (n = 0)	NA	

(*Continued*)

Table 2. (Continued).

Risk factor	Outcome of interest	State of evidence	Research gaps
Years of education (n = 9)	Cognitive function (n = 4)	Evidence suggests that years of education is protective and attenuates racial disparities. One study found a stronger protective effect for AAs versus NHWS with ≥12 years of education.	The key hypothesized biological mechanism for education is cognitive reserve: Education is also associated with health behaviors that lower vascular risks, including not smoking, healthy eating and more physical activity. Only 3 of the 22 studies included in this review examined incident AD, while 13 focused on cognitive function tests. Part of the educational effect observed may be therefore driven by testing bias. Future research should examine the effects on incident AD and explore the potential mediators of the education-AD relationship, including socioeconomic, behavioral and biological/ cognitive reserve pathways.
	Cognitive decline (n = 4)	Education is protective in both race groups. One study found a protective effect for APOE-e4 gene allele carriers only among NHW women .	
	Incident AD or other dementia (n = 2)	Education is predictive of incident AD and may partially attenuate racial disparities.	
Literacy (n = 10)	Cognitive function (n = 6)	Literacy has an effect that may vary by socio-economic position for NHWs but not AAs. Literacy partially or fully attenuates racial disparities.	
	Cognitive decline (n = 3)	Literacy is protective for both race groups and may attenuate racial disparities.	
	Incident AD or other dementia (n = 1)	Literacy is predictive of incident AD in both races, though AAs have lower literacy levels.	
Quality of education (n = 3)	Cognitive function (n = 3)	School quality is associated with cognitive function. The effect differs by race depending on the measure used and geographic location of the study.	
	Cognitive decline (n = 0)	NA	
	Incident AD or other dementia (n = 0)	NA	

Years of education. In bivariate analysis, four studies observed lower education levels among AAs (Barnes et al., 2005; Garcia et al., 2018; Masel et al., 2010; Wilson et al., 2009), and one observed no difference by race (Vásquez et al., 2015). In adjusted analysis for the effect on cognitive function, two studies found that years of education partially attenuated racial disparities (Masel et al., 2010; Vásquez et al., 2015). One study observed that education was protective for both AAs and NHWs (Reuser, Willekens, & Bonneux, 2011), and another found that the protective effect of having more than 12 years of education was stronger in AAs than NHWs, while there was no racial difference in effect at less than 12 years (Barnes et al., 2011). In an examination of cognitive decline, two studies observed the effect of education was equivalently protective in both race groups (Barnes et al., 2005; Vásquez et al., 2015). One study identified a non-linear association where less education was protective against cognitive decline in earlier years, but more education was protective in later years, though this pattern did not vary by race (Wilson et al., 2009). By contrast, another study found that while education was protective in both race groups for those without the genetic risk factor APOE ε4, education is only protective for NHW women with APOE ε4 (Arpawong, McArdle, & Prescott, 2016). Among the two studies that examined the effect on incident dementia, one found

that education attenuated racial disparities (Garcia et al., 2018), while another found that there was no difference by race in incident dementia among those with lower educational attainment (Rodriguez et al., 2018).

These findings suggest that educational attainment is associated with Alzheimer's disease in both races and that the lower educational attainment among the AA population may be an important contributor to racial disparities in Alzheimer's disease.

Literacy. In studies that reported bivariate associations by race, all found that AAs had significantly lower literacy levels than NHWs (Carvalho et al., 2015; Chin, Negash, Xie, Arnold, & Hamilton, 2012; Kaup et al., 2014; Kuczmarski et al., 2015; Manly, Jacobs, Touradji, Small, & Stern, 2002; Sachs-Ericsson & Blazer, 2005). In adjusted analysis of cognitive function, one study observed an association with education and literacy in both races (Kuczmarski et al., 2015). Another study found that literacy level was associated with cognitive function in all AAs, but only NHWs with low socioeconomic status (Dotson, Kitner-Triolo, Evans, & Zonderman, 2009). Four studies examined literacy and education as mediators for the relationship between race and cognitive function, and found that education and literacy combined partially (Manly et al., 2002) or fully (Carvalho et al., 2015; Chin et al., 2012; Crowe et al., 2008) attenuated racial differences in cognitive function.

For rate of cognitive decline, two studies observed that the effect of literacy was protective for both NHWs and AAs (Kaup et al., 2015; Yaffe et al., 2009), while one study found that the relationship between race and rate of decline was mediated by education and literacy (Sachs-Ericsson & Blazer, 2005). For dementia incidence, one study found that literacy level was predictive of dementia in both races (Kaup et al., 2014). These studies suggest that literacy level as an important consideration for racial disparities in Alzheimer's disease risk that may help to account for more of the discrepancy in risk than education alone.

Educational quality. Three studies identified in this review examined markers of school quality (e.g., student-teacher ratios) on cognitive function. One observed an association between school quality and cognitive function that remained after accounting for education and literacy level (Crowe et al., 2013). The association did not differ by race but was only present in those with a high school education or less (Crowe et al., 2013). A second study found that school quality, years of education and late-life literacy each were associated with cognitive function in AAs, while among NHWs there was only an association with late-life literacy and educational quality (Sisco et al., 2015). The third study observed that state of school attendance was associated with cognitive function in both races after accounting for years of education, but the association was stronger in AAs than NHWs in a national sample and stronger in NHWs than AAs in a New York City sample (Liu et al., 2015). We identified no studies in our search that examined the relationship between educational quality and rate of cognitive decline or incident Alzheimer's disease. Combined, these studies suggest that discrepancies in educational quality in combination with years of education and literacy level likely account for some of the observed racial disparities in Alzheimer's disease risk.

2. Obesity

We identified 10 studies that examined the effect of obesity on racial differences in cognition. Three studies reported a bivariate analysis of BMI by race, all of which found mean BMI is higher in AAs than NHWs (Arvanitakis, Capuano, Bennett, & Barnes, 2018; Bressler et al., 2013; Sturman et al., 2008). Among those studies that examined an association with cognitive function, one study found that being overweight or obese was associated with higher cognitive functioning in AAs but not in NHWs (Rajan, Skarupski, Rasmussen, & Evans, 2014), while two found that obesity was associated with lower cognitive function for AAs, but not NHWs (Bryant, Ford, & Kim, 2014; Sturman et al., 2008). One study observed no association between obesity and cognitive function in either race (Reuser et al., 2011). In studies that examined the effect on rate of cognitive decline, one study observed that higher BMI was protective against decline, and that there was no difference by race (Arvanitakis et al., 2018), while another found that the protective effect of obesity was only present in APOE-e4 carriers, regardless of race (Rajan et al., 2014). A third study observed no effect of BMI on cognitive decline in either race (Kaup et al., 2015). A fourth study observed an effect for both races, but only when including those participants who already were cognitively impaired (Sturman et al., 2008). Of the two studies that examined obesity in relation to incident Alzheimer's disease and related dementias, one found that obesity increased the risk of dementia incidence in NHWs, but not AAs (Gottesman et al., 2017) while the second observed a protective effect of obesity for both NHWs and AAs when BMI was equal to 30–34.9, but only for NHWs when BMI was greater than 34.9 (Hu et al., 2012).

One additional study that we included in this review examined if four alleles associated with the fat mass and obesity gene FTO were associated with cognitive function and decline. The authors reported that while AAs had greater genetic risk of obesity, there were no racial differences in its association with cognitive function, while NHWs with genetic risk of obesity faced an increased rate of cognitive decline (Bressler et al., 2013). Our findings reflect the complex relationship between obesity and Alzheimer's disease risk, and demonstrate that there is insufficient evidence to determine if and how obesity plays a role in racial disparities for Alzheimer's disease.

3. Smoking

We identified eight studies that examined the association between smoking and cognitive function or rate of cognitive decline. We did not identify any studies that met our criteria for incident Alzheimer's disease or related dementias. In studies that reported bivariate differences in smoking by race, two studies reported that smokers were more likely to be black (Aggarwal et al., 2006) or black men (Kuczmarski et al., 2015), and one study found smokers were more likely to be white (Knopman et al., 2001). In association with cognitive function, three studies reported no association with smoking (Bachman, Green, Benke, Cupples, & Farrer, 2003; Kuczmarski et al., 2015; Reuser et al., 2011), and one study reported that current smoking was associated with lower cognitive function, but that there was no difference by race (Aggarwal et al., 2006). However, one reported that not smoking, when combined with physical activity, attenuates racial differences in cognitive function by 5% (Vásquez et al., 2015). In analysis of the effect on rate of cognitive decline, one study observed smoking was predictive of cognitive decline in both races (Yaffe et al., 2009), and one study found that smoking was not associated

with rate of cognitive decline in the full sample, but current smokers versus former smokers had faster cognitive decline on one cognitive function test (Knopman et al., 2001). Two additional studies observed no association between smoking and rate of cognitive decline for either race (Kaup et al., 2015; Vásquez et al., 2015). Combined, these studies provide an inconclusive picture of whether smoking contributes to racial disparities.

4. Physical activity

We identified seven studies were identified that examined the role of physical activity in relation to cognitive function and rate of cognitive decline. We did not identify any studies that compared AAs to NHWs in the effect of physical activity on incident Alzheimer's disease. In the five studies that reported bivariate associations by race, all reported that AAs were less likely to participate in moderate and/or vigorous physical activity than NHWs (Masel et al., 2010; Rajan et al., 2015; Vásquez et al., 2015; Zhu et al., 2015, 2017). In adjusted analysis for cognitive function, one study observed a protective effect for physical activity that did not vary by race (Zhu et al., 2015), and two studies observed that physical activity partially mediated racial differences in cognitive function (Masel et al., 2010; Vásquez et al., 2015). By contrast, one study found that for AAs the effect of engaging in 1.25–3.99 h of physical activity per week was similar to that of engaging in >4 h of physical activity per week for NHWs, suggesting a stronger protective effect of physical activity for AAs (Rajan et al., 2015). Rate of cognitive decline was analyzed in four studies, two of which observed a protective effect of physical activity only among NHWs (Rajan et al., 2015; Zhu et al., 2017), one that found the protective effect did not vary by race (Yaffe et al., 2009), and one that found no association in either race (Kaup et al., 2015). These findings suggest that lower physical activity may help to explain some of the differences by race in cognitive function scores, but there is insufficient evidence to know if physical activity contributes to racial disparities in cognitive decline.

5. Psychosocial stress

We identified six studies that examined racial differences in the association of psychosocial stress and cognition. Examples of stress measures were items from the Perceived Stress Scale (Aggarwal et al., 2014), recent major negative life events (Kaup et al., 2015; Sheffler et al., 2014), or self-reported lifetime stressful experiences (Aggarwal et al., 2014; Kaup et al., 2015; Sheffler et al., 2014; Zuelsdorff et al., 2017). In bivariate analysis, three studies reported a higher number of stressful events among AAs compared with NHWs (Aggarwal et al., 2014; Wilson et al., 2005; Zuelsdorff et al., 2017), and one observed comparable levels of stress between AAs and NHWs (Wilson et al., 2005). One study examined the association with cognitive function, finding that the negative effect of stress on cognitive function was stronger for AAs (Zuelsdorff et al., 2017).

Higher levels of stress were associated with faster rate of cognitive decline in four studies (Aggarwal et al., 2014; Kaup et al., 2015; Sheffler et al., 2014; Wilson et al., 2005). There was no difference by race in two studies (Aggarwal et al., 2014; Wilson et al., 2005), but a third study observed that stress only mattered for cognitive decline in NHWs (Kaup et al., 2015). The fourth study found that the rate of cognitive decline was greater among AAs when stress was low, but that there was no difference in rate of decline

between AAs and NHWs when stress was high (Sheffler et al., 2014). For incident Alzheimer's disease, one study found that stress was predictive of Alzheimer's disease for NHWs, but not AAs (Wilson et al., 2005). These findings suggest that psychosocial stress may be an important risk factor for Alzheimer's disease, though there is insufficient evidence to determine if it helps to explain racial disparities.

6. Social isolation

We identified six studies that examined the relationship between social isolation and our cognitive outcomes, though each study measured isolation using different tools and conceptualizations (e.g., self-reported loneliness, measures of degree and types of interpersonal support and social network size). Among studies reporting bivariate associations of isolation and race, one reported slightly higher levels among AAs (Kats et al., 2016), one reported higher levels of isolation among NHWs (Han, Capuano, Barnes, & Bennett, 2016), and a third study observed no difference in the prevalence of isolation by race (Zahodne, Watson, Seehra, & Martinez, 2017). In studies that examined the relationship with cognitive function, three studies found isolation was associated with lower cognitive function but observed no difference in the effect by race (Han et al., 2016; Kats et al., 2016; Zahodne et al., 2017).

In those examining the rate of cognitive decline, one study reported that frequency of social contact is more protective for NHWs than AAs, but that the number of social ties produced no difference in effect by race (Barnes, Mendes de Leon, Bienias, & Evans, 2004). Three studies observed no effect of isolation on rate of cognitive decline in either race group (Kats et al., 2016; Kaup et al., 2015; Yaffe et al., 2009). We did not identify any studies that compared the effect of social isolation on incident Alzheimer's disease or related dementia by race. Broadly, these findings suggest that while social isolation and cognitive function are associated, there is insufficient evidence to determine if social isolation plays a role in racial disparities in any of the cognitive outcomes.

Discussion

We found strong evidence that years of education and literacy help to explain disparities in Alzheimer's disease (AD) risk between NHWs and AAs across measures of cognitive function, rate of cognitive decline and incident AD. We found moderate evidence that school quality and physical activity may help to explain racial disparities in cognitive function. We observed weak or inconclusive evidence for obesity, psychosocial stress, smoking or social isolation in explaining racial disparities in AD risk across all measures of cognition.

Delineating these findings by cognitive function at a single time point, rate of cognitive decline, and incident AD is important to understanding and intervening on racial disparities. Some studies have reported that AAs tend to have lower cognitive function scores, though their rate of cognitive decline is equal to or slower than NHWs (Early et al., 2013; Masel & Peek, 2009; Weuve et al., 2018). As such, the disparities observed might not be due to a faster decline over time among AAs, but lower baseline cognition that results in increased AD incidence at an earlier age.3 Different interventions at different points in the life span may, therefore, help to address racial disparities. Early life interventions may help reduce disparities in baseline differences for the next

generation. Later in life, interventions that slow the rate of decline may preserve cognitive functioning and lower the risk of AD.

About half of the studies in this review focused on the effect of one or more of the six social and behavioral risk factors on cognitive function at a single point in time. While these associational studies may suggest important factors that contribute to differences in baseline cognitive functioning, it is also possible that 1) the risk factors are the result rather than the cause of lower or declining cognitive function or 2) that the observed associations are driven by a third variable. For example, all three of the studies that tested the association of social isolation measured it at the same time as cognitive function (Han et al., 2016; Katz et al., 2012; Zahodne et al., 2017), and the three studies assessing the impact of physical activity on cognitive function measured it at the same time or within 6 months of cognitive assessment (Masel et al., 2010; Vásquez et al., 2015; Zhu et al., 2015). It is possible that both social isolation and exercise were determined by, rather than predictive of, changes in cognition. Alternatively, cognitive function, social isolation, and physical activity may all be influenced by a third variable, such as depression.

By contrast, most of the studies in this review that analyzed rate of cognitive decline had years-long gaps between baseline risks and cognitive testing and adjusted for one's own baseline scores on cognitive function. These studies provide a stronger evidence base for factors that could play a role in how rapidly one's cognition declines, thereby indicating possible opportunities for late-in-life interventions to reduce the risk of AD. Years of education and literacy were the only risk factors examined in this review with consistent evidence in both studies of cognitive function and rate of cognitive decline and/or incident AD.

Another important consideration in study design for this review is the distinction in interpretation of studies that tested for mediation versus moderation to examine racial disparities in the effect of the risk factor on cognitive outcomes. Studies that examined education and/or literacy as a mediator found that differences in cognitive outcomes are partially or fully explained by differences in educational attainment and literacy (Carvalho et al., 2015; Chin et al., 2012; Crowe et al., 2008; Masel et al., 2010; Sachs-Ericsson & Blazer, 2005; Vásquez et al., 2015). Interpreting this finding suggests that the differences in educational attainment and literacy in itself may explain the racial disparity in AD risk. By contrast, one study in this review found evidence for education as a moderator where the beneficial effect of having more than a high school degree was stronger for AAs than NHWs (Barnes et al., 2011). This finding suggests disparities are not merely the result of direct effects of education attained early in life, but that other factors associated with these differences in education may accumulate to enhance the effect of education on AD risk. Studies identified by this review that formally tested for moderation were a minority, indicating a critical gap in the literature, as many different social, behavioral, environmental and biological factors likely interact in producing aging-related disparities (Hill et al., 2015; McDonough & Allen, 2018). This difference in study design and interpretation indicates different possibilities in testing and understanding the possible biological mechanism(s) of the education–AD relationship.

Promising frameworks for exploring education and Alzheimer's disease risk

One of the leading theories to explain the link between education and literacy to Alzheimer's disease broadly is the cognitive reserve hypothesis. The concept of cognitive reserve emerged to help explain why some individuals have fewer clinical symptoms of Alzheimer's disease in the presence of neuropathology compared with others (Stern, 2012). Indeed, some studies that have investigated racial differences in AD pathology in autopsied brains have failed to find clear differences between NHWs and AAs (Riudavets et al., 2006; Sandberg, Stewart, Smialek, & Troncoso, 2001). The hypothesis posits that cognitive stimulation throughout one's life will allow for greater neurocognitive compensation and flexibility, which results in fewer cognitive symptoms when Alzheimer's disease pathology is present (Stern, 2009). The relationship between education and cognitive reserve is assumed to result from greater cognitive stimulation – especially at early ages when the brain is in critical phases of development (Lesuis et al., 2018). While the exact effect of cognitive reserve on brain structure remains an open question, some recent research has found that individuals with higher cognitive reserve had slower early cognitive decline despite gray matter atrophy (Mungas et al., 2018). One study found those with higher cognitive reserve were able to more efficiently activate neural networks needed to perform a range of cognitive tasks (e.g., memory, executive functioning) (Stern, Gazes, Razlighi, Steffener, & Habeck, 2018). Another study found that those with higher cognitive reserve did not require the same high levels of activation and synchronization of neural networks in order to perform memory tasks (Martínez et al., 2018). Combined, these studies suggest that those with cognitive reserve have increased neuro-functioning, yet do not require this efficiency to effectively perform cognitive tasks. While these studies are enlightening, the cognitive reserve hypothesis is based on using education, literacy, IQ as proxies of reserve, under an assumption that these proxies represent an effect of cognitive stimulation (Valenzuela & Sachdev, 2006). However, in most other examinations of the link between education and health disparities, education is often presumed to operate indirectly through its influence on psychosocial wellbeing, access to resources and health behaviors (Adler & Stewart, 2010).

As such, an alternative biological mechanism that may help to explain the relationship between education and AD risk is "weathering." The weathering hypothesis argues that the stressful experiences of racial discrimination and oppression contribute to faster biological aging (Geronimus, 1992; Geronimus et al., 2006). The concept was initially proposed as the mechanism to explain why racial disparities in pre-term birth persist among college-educated AA mothers compared to college-educated NHW mothers – a pattern that challenged the notion that racial disparities were driven largely by socioeconomic disparities (Geronimus, 1992). Weathering is presumed to operate via chronic stress and the over-activation of the hypothalamic pituitary adrenal axis and the sympathetic-adrenal medullary axis – also known as the "fight or flight" response (Booth et al., 2015; McEwen, 2012; Seeman, McEwen, Rowe, & Singer, 2001). As a result, chronic stress produces multiple changes to the metabolic, inflammatory and cardiovascular systems (i.e., allostatic load) that may increase Alzheimer's disease risk both directly through the influence on cognition, and indirectly through its influence on cerebrovascular health (Juster et al., 2010; McEwen, 2012; Snyder et al., 2015). Allostatic load may also contribute directly to

neuroinflammation, resulting in neuronal death and increased risk of AD (Levy Nogueira, Epelbaum, Steyaert, Dubois, & Schwartz, 2016). Thus, the weathering hypothesis could help to explain the finding that education may have a stronger effect on AA cognition than NHW in that the socioeconomic factors associated with lower stress (e.g., income, safe housing, and communities) may be more strongly tied to higher education for AAs than for NHWs.

It is important to note that the limited evidence in this review for psychosocial stress as an explanatory factor for racial disparities in AD does not preclude "weathering" and chronic stress as possible mechanism. The inconsistent findings were from a few studies that used various measures of stress, suggesting more research on weathering and allostatic load might help to clarify the mechanistic pathways of racial disparities in Alzheimer's disease. To date, few studies have looked at the effects of allostatic load and cognitive reserve in concert. To move this research forward, new studies might investigate if and how the concept of allostatic load contributes to our understanding of cognitive reserve, and if the effects of cognitive stimulation and chronic stress interact to influence brain structures and neural processes that counter or reinforce cognitive changes. We also need a broader exploration of how multiple levels of factors may accumulate or interact to drive racial disparities in AD, as outlined in the NIA Health Disparities Research Framework (Hill et al., 2015). Accomplishing this task will require collaborative efforts between neurologists, epidemiologists and social scientists to explore to define the relationships and test interventions that may reduce Alzheimer's disease risk through the identified pathways.

Limitations

This review has several limitations of note. First, we chose to focus on epidemiological studies in an effort to gain a better understanding of the "real life" population distributions of multiple potentially modifiable risk factors. The trade-off of this approach is that all of the evidence identified in this review is observational and associational, limiting causal interpretation from the reviewed findings. Additionally, in an effort to narrow our scope, we based our searches around Alzheimer's disease, cognitive function and rate of cognitive decline as the key outcomes, which did not identify studies focused exclusively on vascular or other types of dementia that also have racial differences and could have contributed to our analysis and interpretation of findings. We also were unable to differentiate or highlight the findings for specific cognitive domains pertinent to AD risks, such as episodic memory and executive functioning, as most of the studies in this review did not report their findings by cognitive domain. This more nuanced approach may have enabled us to detect more specific patterns between the selected risk factors and racial disparities in AD.

We were further limited by the geographic dispersion of available studies. While we did not limit our search geographically, nearly all of the cohorts used in the included studies resided in the south or the industrial northeast/Midwest; both regions have histories of migration and race-based laws and practices that are distinct from other regions, reducing generalizability. Studies that explore mechanisms of racial disparities in Alzheimer's disease and its risk factors with nationally representative cohorts, cohorts residing in the West, and younger cohorts could enhance our findings.

Conclusions

As detailed by Hill et al. (2015), health disparities rarely are the product of singular factors, but rather emerge throughout the life course from a constellation of factors that interact across multiple domains (environmental, sociocultural, behavioral, and biological) (Hill et al., 2015). It is generally recognized that the development of AD requires both a biological risk, such as genetic predisposition, in addition to modifiable risks embedded within environmental, sociocultural and behavioral contexts (McDonough & Allen, 2018). This review synthesized the evidence on modifiable factors that may be distributed differently by race group and that have been linked to AD risk in the general population. These factors map onto the environmental, sociocultural and behavioral domains of the NIA Health Disparities Research Framework, but are far from a comprehensive list of possible factors that could contribute to racial disparities in AD (Hill et al., 2015).

Regardless of the multitude of factors likely at play, however, at the root of all health disparities is the embodiment of social inequality (Ferraro & Shippee, 2009; Krieger, 2005). In the context of education, literacy and AD risk, racial discrimination in the form of Jim Crow laws has contributed to the lower educational attainment – and by extension literacy – for many AA older adults in the studies reviewed. Education is associated broadly with health behaviors and improved access to health-promoting economic, physical and psychosocial resources (Cutler & Lleras-Muney, 2010; Ross & Wu, 1995). Although the de jure segregation of past generations is fortunately in the past, de facto residential segregation and other forms of racism – and their associated effects on education – continue to persist in the US (Kotok, Frankenberg, Schafft, Mann, & Fuller, 2017; Massey & Denton, 1993; Rugh & Massey, 2014). This likely shapes AD risk and disparities for the next generation.

While our findings identified major gaps in knowledge regarding the role of modifiable risk factors in racial disparities, they also provide direction for future research to disentangle the root causes of these disparities and opportunities for risk-reducing intervention and policy efforts. Considering the strong evidence for education and its possible mechanisms, it is especially important to consider both early and late-life interventions surrounding cognitive stimulation and chronic stress at individual, community and policy levels to reduce racial disparities in Alzheimer's disease risk.

Notes

1. For a sample of the search terms used for the 3-step process in PubMed, see Supplemental Table 1.
2. Supplemental Table 2 provides a complete list of geographic research sites and the number of studies published for each site by risk factor.
3. See Supplemental Figure 1.

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Appendix A. Inclusion and exclusion criteria checklist

1. Does the study population include community-dwelling adults who do not have a serious or end-stage illness that influences cognition directly or through treatments (e.g., lupus; cancer), and who are being observed for: a. cognitive impairment no dementia; or b. cognitive decline; or c. Alzheimer's disease	
Yes	Proceed to #2
No	Proceed to #5
2. Does the study examine one or more of the following modifiable risk factors for Alzheimer's disease: education, exercise, stress, isolation, obesity, tobacco/smoking?	
Yes	Proceed to #3
No	Exclude
3. Does the study directly compare and report the effect of one or more of the above listed modifiable risk factors among African Americans versus non-Hispanic white participants for a cognitive outcome?	
Yes	Proceed to #4
No	Exclude
4. Is the study a cross-sectional or cohort observational study?	
Yes	Include
No	Exclude
5. Is the article a review or meta-analysis of risk or protective factors for Alzheimer's disease?	
Yes	Proceed to #6
No	Exclude
6. Include primary studies from the review that meet criteria 1–6.	

APPENDIX B: MANUSCRIPT 2

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Article

State inequality, socioeconomic position and subjective cognitive decline in the United States

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ABSTRACT

Background: Social gradients in health have been observed for many health conditions and are suggested to operate through the effects of status anxiety. However, the gradient between education and Alzheimer's disease is presumed to operate through cognitive stimulation. We examined the possible role of status anxiety through testing for state-level income inequality and social gradients in markers of socioeconomic position (SEP) for Alzheimer's disease risk.

Methods: Using data from the cross-sectional 2015 and 2016 Behavioral Risk Factor Surveillance System (BRFSS) and the U.S. Census Bureau's American Community Survey, we tested for the association between U.S. state-level income inequality and individual SEP on subjective cognitive decline (SCD) – a marker of dementia risk – using a generalized estimating equation and clustering by state.

Results: State income inequality was not significantly associated with SCD in our multivariable model (OR 1.2; 95% CI: 0.9, 1.6; p = 0.49). We observed a clear linear relationship between household income and SCD where those with an annual household income of 50k to 75k had 1.4 (95% CI: 1.3, 1.6) times the odds and those with household incomes of less than $10,000 had 4.7 (95% CI: 3.8, 5.7) times the odds of SCD compared to those with household income of more than $75,000. We also found that college graduates (ref.) and those who completed high school (OR: 1.1; 95% CI 1.04, 1.2) fared better than those with some college (OR: 1.3, 95% CI 1.2, 1.4) or less than a high school degree (OR: 1.5; 95% CI: 1.4, 1.7).

Conclusions: Income inequality does not play a dominant role in SCD, though a social gradient in individual income for SCD suggests the relationship may operate in part via status anxiety.

1. Background

Over the past several decades, researchers have observed a "social gradient in health" where each step down on the social ladder is associated with worse health outcomes – even when comparing different status levels of middle-class office workers (Marmot et al., 1991). This growing body of literature has demonstrated that the influence of socioeconomic position (SEP) on health outcomes is not merely due to the material deprivation among those living in poverty, but may be attributed, in part, to status rankings between individuals (Marmot, 2004; Wilkinson, 1999). Known as the "relative income hypothesis," this pattern in health outcomes is theorized to operate through a psychosocial/stress response to social comparisons (Mullahy, Robert, Wolfe, Robert, & Wolfe, 2011). Additional studies suggest that individuals in societies with higher levels of income inequality may experience an increased sense of social comparison, or "status anxiety," such that income inequality may be an important independent risk factor for health conditions with social gradients beyond what is accounted for by the individual's SEP (Pickett & Wilkinson, 2015).

The association between income inequality and health has been replicated in cross-national comparisons, and in studies that examine differences between U.S. states for a variety of health conditions (Kim, Kawachi, Hoorn, & Ezzati, 2008; Pickett & Wilkinson, 2015; Van Deurzen, Van Ingen, & Van Oorschot, 2015). The status anxiety hypothesis suggests that rising inequality has a direct effect on health via its activation of the body's stress-response system, which produces worse health outcomes (Beckie, 2012; Kondo, Kawachi, Subramanian, Takeda, & Yamagata, 2008; Mishra & Carleton, 2015; Singh-Manoux, Adler, & Marmot, 2003). However, debate continues over if and how income inequality may affect individual health above the effects of

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individual SEP. Several proposed mechanisms may help to explain observed relationships, including the differences in social spending on education and health care, and social support for public health that may prevail in more economically equal societies (Kawachi & Kennedy, 1999). The inequality-health relationship has been observed for a variety of health conditions that could be influenced by stress-response, including life expectancy, cardiovascular health and mental health (Kim et al., 2008; Pickett & Wilkinson, 2015; Van Deurzen et al., 2015). To our knowledge, no one has examined the effect of income inequality on age-related cognitive decline or dementia, though there are pertinent theoretical and practical reasons to do so.

More than 5 million people in the U.S. have been diagnosed with Alzheimer's disease, the most common type of dementia, and it is estimated this will increase to 11.6 million by 2025 (Hebert, Weuve, Scherr, & Evans, 2013). As the number of people living with dementia increases, the demand for dementia care services to help with the declines in cognition and independent functioning that are part of the disease is expected to continue to outpace the capacity of medical and long-term care systems, with substantial financial and health impacts to individuals, families and society (Alzheimer's Association, 2018; De Vugt & Verhey, 2013; Plassman et al., 2007; Richardson, Lee, Berg-Weger, & Grossberg, 2013; World Health Organization, 2012).

Dementia is typically diagnosed through a clinical assessment of changes in cognition that begin to substantially interfere with one's ability to fulfill their daily activities. However, dementia is at the severe end of a continuum of age-related cognitive decline that often begins with self-identified changes in cognitive functioning, or subjective cognitive decline (SCD). SCD may not be detectable by a clinical screening test, though it is increasingly recognized as a reliable predictor of objectively assessed cognitive decline, including among those with higher levels of education who tend to perform better on clinical assessments (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007). Though not all cases of SCD or clinically detectable cognitive decline will progress to dementia, SCD can have meaningful impacts on functional abilities and serves as an important early identifier of those most at risk for dementia (Kaduszkiewicz et al., 2014; Marcos et al., 2016; Mitchell & Shiri-Feshki, 2009; Taylor, Bouldin, & Mcguire, 2018).

A social gradient has been observed for age-related cognitive decline by occupational status and income, though some studies note that these associations are substantially attenuated or nullified after accounting for the effect of education (Anttila et al., 2002; Karp et al., 2004; Staff, Chapko, Hogan, & Whalley, 2016; Zeki Al Hazzouri, Haan, Galea, & Aiello, 2011). Educational attainment is one of the best documented modifiable risks for age-related declines in cognition, and has been shown to have a dose-response relationship with clinically-assessed cognitive outcomes (Beydoun et al., 2014; Xu et al., 2016). The body of evidence for the relationship between cognitive decline and education has largely pointed to a direct effect of cognitive stimulation resulting from education as the underlying mechanism for better late-life cognitive outcomes (Carvalho et al., 2015; Jefferson et al., 2011; Meng & D'Arcy, 2012). Cognitive stimulation is hypothesized to have a protective effect for cognition through promoting "cognitive reserve," or the increased efficiency and capacity of neural networks in the presence of dementia pathology (Stern, 2009). Theoretically, cognitive stimulation is thought to allow for greater cognitive flexibility that allows an individual to continue to function well, even in the presence of dementia-related brain pathologies (Martínez et al., 2018; Meng & D'Arcy, 2012).

However, it is plausible that the effects of education and other markers of SEP on cognitive decline could operate in part through status anxiety. Theoretically, status anxiety contributes to the over-activation of the body's stress response and can result in physiological damage operationalized through a composite of biomarkers that measure allostatic load (McEwen, 2012; Wilkinson & Pickett, 2017). Importantly, allostatic load has direct neurocognitive influences on memory and cognitive functioning that may contribute to the risk of Alzheimer's disease (Booth et al., 2015; Juster, McEwen, & Lupien, 2010; Lesuis et al., 2018). Examining the relationship between cognitive decline, inequality and individual markers of SEP may therefore help to shed light on the underlying mechanism between the SEP-cognitive decline relationship, and provide additional evidence for or against the role of inequality in health, and the debated status anxiety hypothesis.

The aim of this study was to test for an association between subjective cognitive decline (SCD) as an early predictor of dementia risk, measures of individual SEP, and state-level income inequality in the U.S. We hypothesize finding evidence for status anxiety hypothesis via presence of a social gradient in markers of individual SEP, and that higher state-level income inequality will be associated with higher odds of SCD after controlling for individual-level SEP. Additionally, this study conducted a secondary examination of status anxiety by modeling an interaction between individual income and income inequality to see if those with lower household income would be negatively affected by income inequality to a greater degree than those with higher household income. Theoretically, a social gradient in the markers of SEP – especially income – and a relationship between income inequality and cognitive decline would support the hypothesis that income inequality impacts health through the psychosocial pathway of status anxiety. If these relationships are not observed, alternative mechanisms should be considered to explain the observed social gradients in health, which for cognitive decline and Alzheimer's disease risk may be cognitive stimulation.

2. Methods

2.1. Data sources

We used the Cognitive Decline module from the 2015 and 2016 Behavioral Risk Factor Surveillance System (BRFSS). The BRFSS is a cross-sectional telephone survey conducted annually by the United States Centers for Disease Control and Prevention that collects self-reported health information from community-dwelling adults (Centers for Disease Control and Prevention, 2016b). The cognitive decline module was asked of all participants age 45 or older who resided in a state that elected to participate in the module. All states except Pennsylvania and Washington D.C. participated in the cognitive decline module in 2015 or 2016. New Jersey, New York, Oregon, Tennessee and Utah participated in the cognitive decline module in both years; for these states we included only the 2016 participants, providing a total of 50 clusters (49 states and Washington D.C.). Puerto Rico participated in 2015, but was excluded from analysis because it is an outlier on our key variables of interest; Puerto Rico has substantially lower household income (median US$19,606) and slightly higher income inequality (Gini coefficient = 0.542; U.S. state min/max = 0.408, 0.535) than any U.S. state (United States Census Bureau, 2016).

2.2. Subjective cognitive decline

The primary outcome of this study was the dichotomized response to an item measuring subjective cognitive decline (SCD), obtained from the BRFSS cognitive decline module. Participants were classified as having SCD if they responded yes to the question: "During the past 12 months, have you experienced confusion or memory loss that is happening more often or is getting worse?".

2.3. Individual socioeconomic position

We used variables from the BRFSS for household income, education and home ownership as markers of SEP. Income was provided in 8 categories ranging from < $10,000 to ≥$75,000; the highest income category was modeled as the reference. Education was categorized as

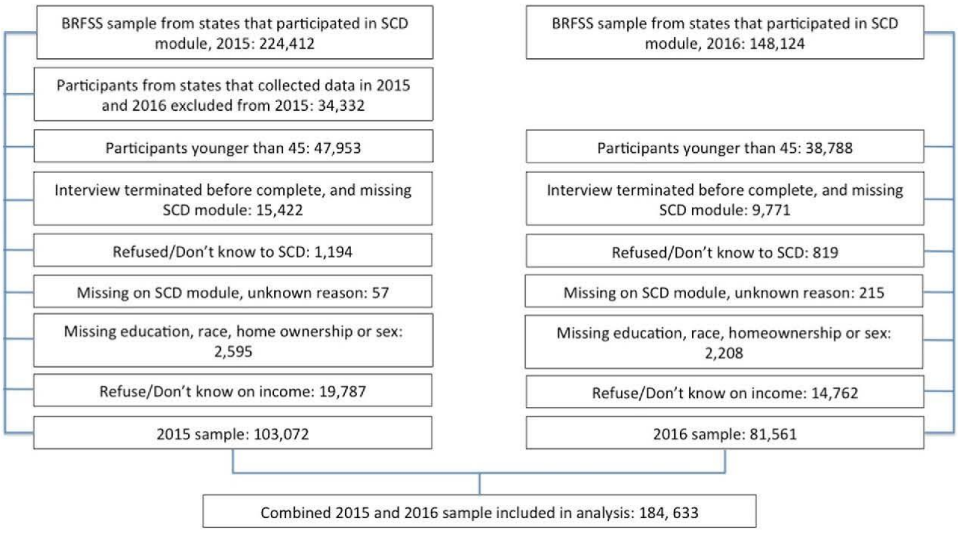

Fig. 1. Primary analysis inclusion and exclusion criteria for study participants who resided in states that participated in the Behavioral Risk Factor Surveillance System cognitive decline module in 2015 or 2016. Multiple imputation was conducted in sensitivity analysis to account for missing data.

less than high school, high school graduate, some college or technical school, and college or technical school graduate, with the highest education category as the reference. Homeownership was modeled as a dichotomous variable with owners as the reference.

2.4. State-level income inequality

As a measure of states' income inequality, we used the Gini coefficients based on the 2015 and 2015 American Community Survey (ACS), an annual survey of about 3.5 million households (United States Census Bureau, 2015). This indicator, published by the U.S. census bureau, is one of the most commonly used measures of income inequality. Its value ranges from 0 (complete equality) to 1 (one household captures all income); (De Maio, 2007).

2.5. Individual covariates

Adjusted models controlled for gender, age and race/ethnicity, provided by the BRFSS. Race/ethnicity was categorized as non-Hispanic white (reference), non-Hispanic black, Hispanic/Latino, Asian, and an "other" category comprised of respondents who reported their race as American Indian/Alaska Native, Pacific Islander/Hawaiian, mixed race or other. Age was modeled categorically at 45–49 (reference); 50–59; 60–69; 70–79; and top-coded at ≥80 years, as available in the BRFSS.

2.6. Statistical analysis

We matched the 2015 and 2016 BRFSS datasets with 2015 and 2016 income inequality data from the ACS, respectively (United States Census Bureau, 2015, 2016). In the primary analysis, we included participants of the cognitive decline module who had valid responses for age, sex, race/ethnicity, education, home-ownership and income. We calculated weighted proportions of demographic and health characteristics of participants based on SCD status and used chi-square tests to compare the demographic characteristics of those with SCD to those without SCD.

To test for the effects of individual SEP and state-level income inequality on SCD, we used a Generalized Estimating Equation (GEE) with a logit link and independent working covariance, clustered by the participant's state of residence to fit unadjusted and adjusted models. Using a GEE model allowed us to specify the nested nature of the data within each U.S. state and account for heterogeneity of income inequality between states. The GEE provides an average estimate of effect of SCD for the population. This interpretation is in contrast to multilevel models, which estimate the effect for a specific participant, conditional on the covariates in the model, including the state (Hubbard et al., 2010). Some methodologists argue that the population averaged model (GEE) is more appropriate when the research question focuses on neighborhood or state effects (Hubbard et al., 2010).

We tested for effect modification of household income grouped at 3 levels with state-level income inequality to examine if the impact of income inequality varies depending on one's income, by including an interaction term. We also performed two sensitivity analyses. First, we recalculated our analysis use lagged Gini coefficients from 2005 and 2010, computed by the Census Bureau based on 5 years of ACS data (United States Census Bureau, 2015). While these models are more likely to result in state level misclassification (individuals are more likely to move between states within 5 years or 10 years than 1 year), it also has the strength of capturing the contextual effect of income inequality, which may take years to influence health. Second, we conducted multiple imputation using chained equations to account for the high degree of missing data on income. Of the 223,985 participants of the SCD module in 2015 and 2016, 2.1% were missing information on education, race, homeownership or sex, and 15.4% were missing household income data. We performed 200 imputations with all variables from the primary model. We also included variables from the BRFSS dataset that are conceptually or empirically linked with missing income data and that were correlated with income at ≥ 0.3: internet use in the past 30 days, 30-day self-reported health, marital status and employment status (Azur, Stuart, Frangakis, & Leaf, 2011).

Appropriate population weights provided by the BRFSS were applied in all models following guidance available on the BRFSS website (Centers for Disease Control and Prevention, 2016a). Application of these weights adjusts each state's participant sample so it is representative of its population. All analyses were conducted in Stata 14.2 (College Station, TX).

Table 1
Demographic characteristics of adults aged 45 and older as a function of Subjective Cognitive Decline[a] status, Behavioral Risk Factor Surveillance System 2015 and 2016.

	SCD N = 19,662 Weighted %	No SCD N = 164,971 Weighted %	p-value[b]
Household Income ($US)			
≥$75,000	6.0	94.0	< 0.001
≥$50,000 & < $75,000	8.6	91.4	
≥$35,000 & < $50,000	10.4	89.6	
≥$25,000 & < $35,000	13.7	86.3	
≥$20,000 & < $25,000	15.3	84.7	
≥$15,000 & < $20,000	17.4	82.6	
≥$10,000 & < $15,000	21.2	78.8	
< $10,000	26.3	73.7	
Years of Education			
College Graduate	7.0	93.0	< 0.001
Some College	11.5	88.5	
High School Graduate	11.8	88.2	
Less than High School	18.7	81.3	
Homeowners	10.0	90.0	< 0.001
Non-homeowners	17.4	82.6	
Female	11.1	88.9	0.55
Male	11.4	88.6	
Age			
45–50	9.7	90.3	< 0.001
50–59	11.1	88.9	
60–69	10.4	89.6	
70–79	11.9	88.1	
80+	16.6	83.4	
Race/Ethnicity			
Non-Hispanic White	10.9	89.1	< 0.001
Non-Hispanic Black	13.0	87.0	
Hispanic	11.6	88.4	
Asian	6.0	94.0	
Other	17.6	82.4	

[a] Self-reported experience with confusion or memory loss that is happening more often or getting worse in the last 12 months.
[b] X^2 test, adjusted for sampling weights

3. Results

Of the 223,985 who completed the cognitive decline module, 184,633 had complete data and were included in the primary analyses (Fig. 1). On average, participants who were older, had less than a college or technical school education, were not non-Hispanic white or Asian and were not homeowners were more likely to report SCD (Table 1). Additionally, 52.1% of those without SCD reported a household income of more than $50,000 a year, compared to 30.2% of those with SCD.

In the primary analysis, we did not find a statistically significant association between state-level income inequality and SCD, though the odds ratio was in the direction predicted. In unadjusted analysis, the odds of SCD increased 1.2 (95% CI: 0.9, 1.5; p = 0.18) times for each 0.1 unit increase in income inequality, as measured by the Gini coefficient (Table 2). Similarly, in adjusted analyses, the odds ratio for income inequality was 1.2 (95% CI: 0.9, 1.6; p = 0.28). The predicted probability of SCD for those in the most equal state (Gini = 0.408) was 0.09, compared to the least equal state (Gini = 0.535) at 0.11. Overall, the change in predicted probabilities for or every .05 unit increase in the Gini coefficient resulted in less than a 1%-point increase in the predicted probability of SCD, when all covariates were at their mean levels. However, all three measures of SEP (household income, education and home ownership) were protective for SCD. Our results for household income reflected a social gradient in health, with an increasing stepwise protective effect for each higher income category. Compared to those with a household income of more than $75,000 a year, participants with household incomes between $50,000 and $75,000 were 1.4 (95% CI: 1.3, 1.6) times more likely to report SCD, while those with household incomes of less than $10,000 per year were 4.7 (95% CI: 3.8, 5.7) times more likely to report SCD. Higher education also was a protective factor for SCD, though the pattern was not consistent. Compared with college or technical school graduates, those with less than high school had the highest odds of SCD at 1.5 (95% CI: 1.4, 1.7) times, high school graduates had 1.1 (95% CI: 1.0, 1.2) times the odds, and those with some college or technical school had 1.3 (95% CI: 1.2, 1.4) times the odds. Compared with homeowners, those who rented or had another living arrangement were 1.2 (95% CI: 1.1, 1.3) times more likely to report SCD.

We found no evidence of effect modification between income inequality and household income, indicating that the effect of income inequality on SCD does not vary by household income level (Table 3). Additionally, our sensitivity models that examined separately the effect

Table 2
Association of state-level income inequality (Gini coefficient), individual socioeconomic position and subjective cognitive decline* from the Behavioral Risk Factor Surveillance System 2015 and 2016.

	2015–2016 Gini, matched to BRFSS year		
	OR	95% CI	p-value
State income inequality (unadjusted)[a]	1.19	0.92, 1.56	0.19
State income inequality(adjusted)[a]	1.19	0.87, 1.62	0.281
Household Income			< 0.001
≥$75,000	Ref		
≥$50,000 & < $75,000	1.40	1.26, 1.56	
≥$35,000 & < $50,000	1.67	1.53, 1.83	
≥$25,000 & < $35,000	2.22	1.91, 2.58	
≥$20,000 & < $25,000	2.50	2.11, 2.98	
≥$15,000 & < $20,000	2.81	2.35, 3.37	
≥$10,000 & < $15,000	3.52	3.97, 4.17	
< $10,000	4.66	3.79, 5.74	
Education			< 0.001
College or technical school graduate	Ref		
Some college	1.30	1.22, 1.39	
High school graduate	1.12	1.04, 1.21	
Less than High School	1.51	1.36, 1.68	
Non-homeowners	1.19	1.07, 1.33	0.002

Adjusted ORs control for age, race and sex.
[a] OR is based on a 0.1 unit change in Gini coefficient.
* Self-reported experience with confusion or memory loss that is happening more often or getting worse in the last 12 months.

Table 3
Effect of state-level income inequality (Gini coefficient) on subjective cognitive decline* at each level household income (inequality x income) from the Behavioral Risk Factor Surveillance System 2015 and 2016.

	OR	95% CI	p-value
State income inequality[a]			0.43[c]
≥$75,000	1.18	0.74, 1.90	
≥$35,000 & < $75,000	1.40	0.80, 2.44	
< $35,000	1.12	0.86, 1.45	
Education			< 0.001
College or Technical School Graduate	Ref.		
Some College	1.30	1.22, 1.39	
High School Graduate	1.15	1.05, 1.25	
Less than High School	1.67	1.49, 1.87	
Non-homeowners	1.30	1.17, 1.45	< 0.001

Model controls for age, race and sex.
[a] OR is based on a 0.1 unit change in Gini coefficient.
* Self-reported experience with confusion or memory loss that is happening more often or getting worse in the last 12 months.
[c] P-value for the test of the state income inequality by household income.

of the ACS 5- and 10-year lagged Gini coefficients produced comparable results to our original findings (see Table 4 in supplementary materials). The results of our multiple imputation sensitivity analysis were also comparable to our primary analysis (see Table 5 in supplementary materials), indicating the robustness of our findings in spite of substantive missing data on income.

4. Discussion

4.1. Summary of findings

The primary objective for this study was to examine the relationship between state-level income inequality, markers of individual SEP and SCD. We hypothesized that income inequality would be positively associated with SCD after accounting for individual-level SEP. We did not observe a statistically significant relationship between state-level income inequality and SCD in the models tested. While the effect was in the direction predicted, it was substantively small and statistically insignificant. However, we did observe a clear and statistically significant social gradient in health where odds of SCD decreased for each step higher of household income. We also observed significant positive associations for SCD with homeownership and higher education.

4.2. Interpretation

Our findings suggest that income inequality in itself may not have a substantial influence on SCD and dementia risk. This finding reinforces some of the critiques of the income inequality hypothesis. Specifically, critics have argued that any observed relationships between income inequality and health are not likely resulting from a direct effect, but rather income inequality is more likely a mediator in the relationship between other structural processes and health, such as the social distribution of public goods and services (Mellor & Milyo, 2001; Mullahy et al., 2011). Accordingly, many critics also argue that non-psychosocial factors that have a material impact on individual health, such as neighborhood poverty level and race-based residential segregation, may better explain the observed effects (Goldthorpe, John, 2010; Lynch, 2000; Massey & Denton, 1993; Mullahy et al., 2011). Correspondingly, many studies on dementia risk point to the unequal distribution of education across race and class lines as a key explanatory mechanism of disparities in dementia risk, operating via cognitive stimulation (Beydoun et al., 2014; Chin, Negash, Xie, Arnold, & Hamilton, 2012; Crowe et al., 2013; Jefferson et al., 2011; Kaup et al., 2014).

However, while income inequality may not be an important risk factor for SCD, our findings do not preclude the possible role of status anxiety and the psychosocial pathway for individual dementia risk. We observed relatively large and significant differences in odds of SCD, even among those in the top income categories, as would be expected if status anxiety were an operating mechanism. Additionally, our findings for the association between education and SCD suggest that social status, rather than cognitive stimulation, may be a contributing mechanism for the dementia-education association. Specifically, we observed that graduates of college or technical school and high school fare better than non-completers of either degree. If cognitive stimulation were the dominant mechanism in the relationship between education and dementia risk, as posited by the cognitive reserve hypothesis, more years of education among those who started but did not complete college or technical school should theoretically have a stronger protective effect than what is observed among high school graduates. The effect of education operating as a potential status marker rather than via cognitive stimulation is also supported by findings from some studies from low- and middle-income countries where average education and literacy levels are low, and there is not a clear link between education and dementia (Chandra et al., 2001; Hall, Gao, Unverzagt, & Hendrie, 2000).

Overall, our findings indicate that dementia risk may not be influenced by income inequality, or exclusively determined by early life factors such as education. Rather, it is possible that the effects of both education and income on dementia risk operate, in part, through social comparisons that may be fueled by resource distribution and other forms of structural inequalities that extend beyond the distribution of income. However, it is also possible that these findings reflect other mechanisms shaped by income and education, such as health behaviors.

4.3. Methodological considerations

The literature linking. income inequality to health is mixed, and frequently dependent upon study design (Kragten & Rözer, 2017), the geographic unit of measurement (Pickett & Wilkinson, 2015), and accurately accounting for the state-level factors that may confound the relationship (Kondo et al., 2009). Our study design and analyses took into account the effect of state context of income inequality, and U.S. states have been observed as sufficiently large and heterogeneous to be sensitive to an effect of income inequality as measured by the Gini coefficient, while counties or cities are often too small to be sensitive to an effect (Bernabé & Marcenes, 2011; Pabayo, Kawachi, & Gilman, 2014; Pickett & Wilkinson, 2015). However, there may be other unmeasured state-level factors that confound the relationship between income inequality and SCD that we could not include in our models, such as state variation in the provision of social services (Bradley et al., 2016). Furthermore, recent research suggests that in some cases the Gini coefficient may not be as sensitive to the effects of income inequality on health as are other markers of inequality, such as the income share of the top 1% or 5% (Hill & Jorgenson, 2018). The key difference between income shares and the Gini coefficient is in the ability to account for income inequality at the very top and bottom of the income distribution. Because the Gini coefficient is less sensitive to inequalities at the tail ends of the income distribution, geographies with substantially different income distributions theoretically could have similar Gini coefficients (Palma, 2011).

4.4. Limitations

Our study had several limitations. First, we were unable to determine the temporal ordering of the relationship between SCD and markers of SEP due to the cross-sectional design. While educational attainment is often established early in the life course, both income and cognition tend to decline as individuals age. In this study it was impossible to know if SCD predated or contributed to lower income levels, such as through early retirement resulting from cognitive decline. A second limitation was in the restricted availability of household income data. Income in the BRFSS is top-coded at $75,000, limiting our ability to examine if the social gradient we observed between SCD and income continues in a linear fashion for those with income levels above $75,000, or plateaus after a particular threshold of household income. A third key limitation in this analysis was in our inability to account for an adequate lag time or a cumulative exposure of state-level income inequality. While our sensitivity analysis demonstrated similar effects of the Gini coefficient when averaged at 5 and 10 years prior to our outcome, our concern over state misclassification (the BRFSS does not provide information on length of state residence or prior state of residence) discouraged us from examining longer lagged effects that may be influential in dementia risk.

4.5. Future directions

The income gradient and protective effect of completing educational degrees evidenced in this study adds to the body of knowledge for dementia risk, suggesting that income and the effects of status anxiety may be important to consider for dementia risk in addition to the effects of education and cognitive stimulation. Future studies should further examine the role of income inequality, individual SEP and status

anxiety on dementia risk in datasets with more explicit measures of perceived social status and employing alternative measures of income inequality. Additionally, cohort studies with available biomarkers for allostatic load or brain imaging would allow for more direct examination and comparison of the effect of individual SEP and income inequality on status anxiety and cognitive reserve as hypothesized mechanisms of dementia risk. A third avenue for exploration is in how the effect of income-based policies and programs throughout the life course shape exposure to income inequality and age-related cognition decline. Already, there is some evidence for a protective effect of late-in-life income beyond the effects of earlier life income for dementia risk (Anttila et al., 2002; Ayyagari & Frisvold, 2016). Future studies could further clarify the role and timing of income-based interventions for reducing the risk of dementia.

In the absence of effective prevention or treatment for dementia, early interventions that target the modifiable risk factors for cognitive decline are the only available strategy for addressing a dementia epidemic (Fink et al., 2018; Livingston et al., 2017). As the population ages and more individuals are at risk of age-related cognitive decline, all plausible possibilities for risk reduction should be considered. A recent report from the Lancet Commission on Dementia Prevention, Intervention, and Care called for researchers and health care providers to "be ambitious" about dementia by reducing known risk factors (Livingston et al., 2017). Increasing income and lowering chronic stress may prove to be a central and important part of an ambitious approach to reduce the risk of dementia.

Author declaration

None.

Note

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflicts of interest

None of the authors have any conflicts of interest or funding sources to disclose for this study.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ssmph.2019.100357.

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APPENDIX C: NSHAP RESTRICTED DATA ACQUISTION

ICPSR | INTER-UNIVERSITY CONSORTIUM FOR POLITICAL AND SOCIAL RESEARCH

ICPSR 20541

National Social Life, Health, and Aging Project (NSHAP): Wave 1

Restricted Data Use Agreement

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National Social Life, Health, and Aging Project (NSHAP): Wave 1

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National Social Life, Health and Aging Project

The NSHAP data is not available for web download at this time as it is covered under a restricted use agreement with the University of Chicago.

Upon receipt of the following documents a copy of the data can be sent:

1) A copy of your IRB approval for the use of the data in whatever project you require the data for. This will typically fall under an Exempt 4 classification for secondary data analysis.

2) A data protection plan (with original signature(s)), which is essentially a written description of how the NSHAP data will be stored on your site and how the data will be protected from unauthorized access on your computer network.

3) The signed data use agreement (with original signature(s)). Email requests can be accepted.

Please use the "Instructions for Preparing the NSHAP Data Protection Plan" as a template/guide in formulating YOUR plan for storage and protection. Sign this document and send it along with your IRB and DUA.

Instructions for Preparing the NSHAP Data Protection Plan

Purpose of the Data Protection Plan: The fundamental goal of the protections outlined in this plan is to prevent persons who are not signatories to the Restricted Data Use Agreement or the Supplemental Agreement With Research Staff from gaining access to the data. The agreement will not be executed if the plan is not written with sufficient specificity, or if data protections are not deemed adequate by ICPSR.

What should be covered by the plan: The Data Protection Plan applies to both the raw data file received from ICPSR as well as any copies made by the research team, and any new data derived solely or in part from the raw data file. The plan also should address how computer output of direct data listings of the files will be kept secure.

Components of the plan: Your Data Protection Plan SHOULD contain the following components:

1. Make reference to Title of Research Project and Principal Investigator(s).
2. List and describe all locations where copies of the data will be kept.
3. Describe the computing environment in which the data will be used:
    - Computing platform (PC, workstation, mainframe platform) ○ Number of computers on which data will be stored or analyzed ○ Whether personal computers used in the research project will be attached to a network or will operate independently (stand-alone)
    - Physical environment in which computer is kept (e.g., in room with public access, in room locked when not in use by research staff)
4. List and describe how data will be stored: (e.g., on PC hard drive, on removable storage media such as CD, diskettes, or Zip(R) drive.)
5. Describe methods of data storage when data are not being used.
6. Describe methods of transmitting the data between research team members (if applicable).
7. Describe methods of storage of computer output (in electronic form as well as on paper).

Types of protection expected: Although there are alternative ways to assure security for the data and applicants should prepare their plans in a manner that best meets their needs, some or all of the following features are typically found in successful data protection plans:

- Password protection for all files containing data (note that password protection is not regarded as sufficient protection by itself)

- Removable storage media holding the data (e.g., CDs, diskettes, zip disks, etc.) kept in a locked compartment/room when not in use
- Stored in a locked compartment/room when not in use
- No transmittal of data or analysis output derived from the data via e-mail, e-mail attachments, or FTP (either over the Internet, an Intranet system, or within a local area network)
- No backup copies of the data to be made
- Data stored in strongly encrypted form

Wherefore, **User** and Responsible Party hereby accepts responsibility for ensuring that the precautions formulated in their Data Protection Plan will be followed by signing and providing the information below:

Name (printed): Scott Carvajal

Signature: 

Institution: University of Arizona

Mailing Address: 1295 N. Martin Ave. PO Box 245209

Tucson, AZ 85724

Email Address: scott.carvajal@arizona.edu

Date: Oct. 15, 2018

Questions and/or completed data protection plans with **original signatures** should be emailed along with DUA and IRB to icpsr-nacda@umich.edu.

National Social Life, Health and Aging Project

This data use agreement is between **ICPSR** and the individual signing the agreement, hereafter referred to as **User**.

Whereas, the **NSHAP** data contain certain information **User** wishes to use for research, public health, or health care operations as permitted under 42 C.F.R. 164.514(e), **User** agrees as follows:

a. Not to use or further disclose the Limited Use **NSHAP** Data Set or any information contained therein other than as permitted by this agreement or required by applicable law.

b. To use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this agreement.

c. To report to ICPSR any use or disclosure of the Limited Use **NSHAP** Data Set or any part of it not provided for by this agreement of which **User** becomes aware.

d. Not to use the information contained in the Limited Use **NSHAP** Data Set to identify the individual whose information is contained in the Limited Use **NSHAP** Data Set, nor to contact them under any circumstances.

e. In the event **ICPSR** becomes aware of any use of the Limited Use **NSHAP** Data Set or any part of it that is not authorized under this agreement or required by applicable law, it may (i) terminate this agreement upon notice; (ii) disqualify the **User** from receiving protected health information in the future; and/ or (iii) report the inappropriate use or disclosure to the Secretary of the Department of Health and Human Affairs. Further sanctions may apply under 42 C.F.R. parts 160 and 164.

ICPSR and the **NACDA** Program on Aging will use the **User** information to create a registry to be used for quality assurance, bench marking and research follow-up with appropriate permission and in accordance with the requirements of the "Common Rule" 45 CFR 46 and the Privacy regulations 45 CFR 160 and 164.

The **User** agrees to provide **ICPSR** with information regarding the use of the **NSHAP** data for publications, seminars, conference papers, and other research related outcomes to be added in the bibliography of use that **ICPSR** maintains for all studies in its collections.

The Responsible Party **User** or PI proposing or supporting the use of the **NSHAP** data for research, must be a faculty level PI, a Research Scientist or have a similar full time appointment at a University, College or Research Center. Graduate students interested in using **NSHAP** for thesis development or research purposes must obtain the signature of their faculty advisor as the responsible Party **User**.

The **NSHAP** data must be maintained in a secure location. No duplication of the data for further distribution is allowed under this agreement. The data can not be placed upon an unsecured computer network for analysis.

Wherefore, **User** and Responsible Party hereby accepts and agrees to these terms by signing and providing the information below.

Name (printed): Scott Carvajal

Signature: 

Institution: Univeristy of Arizona

Mailing Address: 1295 N. Martin Ave., PO Pox 245209

Tucson, Arizona 85724

Email Address: scott.carvajal@arizona.edu

Date: Oct. 15, 2018

The following individuals (the "Authorized Parties") are authorized by the Responsible Party **User** to use the Limited Use **NSHAP** Data Set or any part of it on behalf of **UM** or **USER** and agree to abide by the terms of this Agreement:

Name: Rachel Peterson Signature: 

Name:_____ Signature:_____

Name:_____ Signature:_____

Completed form with **original signatures** should be emailed to icpsr-nacda@umich.edu.

ICPSR | INTER-UNIVERSITY CONSORTIUM FOR POLITICAL AND SOCIAL RESEARCH

ICPSR 34921

National Social Life, Health, and Aging Project (NSHAP): Wave 2 and Partner Data Collection

Restricted Data Use Agreement

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National Social Life, Health, and Aging Project (NSHAP): Wave 2 and Partner Data Collection

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2. List and describe all locations where copies of the data will be kept.
3. Describe the computing environment in which the data will be used:
    - Computing platform (PC, workstation, mainframe platform) ○ Number of computers on which data will be stored or analyzed ○ Whether personal computers used in the research project will be attached to a network or will operate independently (stand-alone)
    - Physical environment in which computer is kept (e.g., in room with public access, in room locked when not in use by research staff)
4. List and describe how data will be stored: (e.g., on PC hard drive, on removable storage media such as CD, diskettes, or Zip(R) drive.)
5. Describe methods of data storage when data are not being used.
6. Describe methods of transmitting the data between research team members (if applicable).
7. Describe methods of storage of computer output (in electronic form as well as on paper).

Types of protection expected: Although there are alternative ways to assure security for the data and applicants should prepare their plans in a manner that best meets their needs, some or all of the following features are typically found in successful data protection plans:

- Password protection for all files containing data (note that password protection is not regarded as sufficient protection by itself)

- Removable storage media holding the data (e.g., CDs, diskettes, zip disks, etc.) kept in a locked compartment/room when not in use
- Stored in a locked compartment/room when not in use
- No transmittal of data or analysis output derived from the data via e-mail, e-mail attachments, or FTP (either over the Internet, an Intranet system, or within a local area network)
- No backup copies of the data to be made
- Data stored in strongly encrypted form

Wherefore, **User** and Responsible Party hereby accepts responsibility for ensuring that the precautions formulated in their Data Protection Plan will be followed by signing and providing the information below:

Name (printed): Scott Carvajal

Signature: 

Institution: University of Arizona

Mailing Address: 1295 N. Martin Ave. PO Box 245209

Tucson, AZ 85724

Email Address: scott.carvajal@arizona.edu

Date: Oct. 15, 2018

Questions and/or completed data protection plans with **original signatures** should be emailed along with DUA and IRB to icpsr-nacda@umich.edu.

National Social Life, Health and Aging Project

This data use agreement is between **ICPSR** and the individual signing the agreement, hereafter referred to as **User**.

Whereas, the **NSHAP** data contain certain information **User** wishes to use for research, public health, or health care operations as permitted under 42 C.F.R. 164.514(e), **User** agrees as follows:

a. Not to use or further disclose the Limited Use **NSHAP** Data Set or any information contained therein other than as permitted by this agreement or required by applicable law.

b. To use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this agreement.

c. To report to ICPSR any use or disclosure of the Limited Use **NSHAP** Data Set or any part of it not provided for by this agreement of which **User** becomes aware.

d. Not to use the information contained in the Limited Use **NSHAP** Data Set to identify the individual whose information is contained in the Limited Use **NSHAP** Data Set, nor to contact them under any circumstances.

e. In the event **ICPSR** becomes aware of any use of the Limited Use **NSHAP** Data Set or any part of it that is not authorized under this agreement or required by applicable law, it may (i) terminate this agreement upon notice; (ii) disqualify the **User** from receiving protected health information in the future; and/ or (iii) report the inappropriate use or disclosure to the Secretary of the Department of Health and Human Affairs. Further sanctions may apply under 42 C.F.R. parts 160 and 164.

ICPSR and the **NACDA** Program on Aging will use the **User** information to create a registry to be used for quality assurance, bench marking and research follow-up with appropriate permission and in accordance with the requirements of the "Common Rule" 45 CFR 46 and the Privacy regulations 45 CFR 160 and 164.

The **User** agrees to provide **ICPSR** with information regarding the use of the **NSHAP** data for publications, seminars, conference papers, and other research related outcomes to be added in the bibliography of use that **ICPSR** maintains for all studies in its collections.

The Responsible Party **User** or PI proposing or supporting the use of the **NSHAP** data for research, must be a faculty level PI, a Research Scientist or have a similar full time appointment at a University, College or Research Center. Graduate students interested in using **NSHAP** for thesis development or research purposes must obtain the signature of their faculty advisor as the responsible Party **User**.

The **NSHAP** data must be maintained in a secure location. No duplication of the data for further distribution is allowed under this agreement. The data can not be placed upon an unsecured computer network for analysis.

Wherefore, **User** and Responsible Party hereby accepts and agrees to these terms by signing and providing the information below.

Name (printed): Scott Carvajal

Signature: 

Institution: Univeristy of Arizona

Mailing Address: 1295 N. Martin Ave., PO Pox 245209

Tucson, Arizona 85724

Email Address: scott.carvajal@arizona.edu

Date: Oct. 15, 2018

The following individuals (the "Authorized Parties") are authorized by the Responsible Party **User** to use the Limited Use **NSHAP** Data Set or any part of it on behalf of **UM** or **USER** and agree to abide by the terms of this Agreement:

Name: Rachel Peterson Signature: 

Name:_____ Signature:_____

Name:_____ Signature:_____

Completed form with **original signatures** should be emailed to icpsr-nacda@umich.edu.

ICPSR | INTER-UNIVERSITY CONSORTIUM FOR POLITICAL AND SOCIAL RESEARCH

ICPSR 36873

National Social Life, Health and Aging Project (NSHAP): Wave 3

Linda Waite
University of Chicago

Restricted Data Use Agreement

Inter-university Consortium for
Political and Social Research
P.O. Box 1248
Ann Arbor, Michigan 48106
www.icpsr.umich.edu

National Social Life, Health and Aging Project

The NSHAP data is not available for web download at this time as it is covered under a restricted use agreement with the University of Chicago.

Upon receipt of the following documents a copy of the data can be sent:

1) A copy of your IRB approval for the use of the data in whatever project you require the data for. This will typically fall under an Exempt 4 classification for secondary data analysis.

2) A data protection plan (with original signature(s)), which is essentially a written description of how the NSHAP data will be stored on your site and how the data will be protected from unauthorized access on your computer network.

3) The signed data use agreement (with original signature(s)). Email requests can be accepted.

Please use the "Instructions for Preparing the NSHAP Data Protection Plan" as a template/guide in formulating YOUR plan for storage and protection. Sign this document and send it along with your IRB and DUA.

Instructions for Preparing the NSHAP Data Protection Plan

Purpose of the Data Protection Plan: The fundamental goal of the protections outlined in this plan is to prevent persons who are not signatories to the Restricted Data Use Agreement or the Supplemental Agreement With Research Staff from gaining access to the data. The agreement will not be executed if the plan is not written with sufficient specificity, or if data protections are not deemed adequate by ICPSR.

What should be covered by the plan: The Data Protection Plan applies to both the raw data file received from ICPSR as well as any copies made by the research team, and any new data derived solely or in part from the raw data file. The plan also should address how computer output of direct data listings of the files will be kept secure.

Components of the plan: Your Data Protection Plan SHOULD contain the following components:

1. Make reference to Title of Research Project and Principal Investigator(s).
2. List and describe all locations where copies of the data will be kept.
3. Describe the computing environment in which the data will be used:
    - Computing platform (PC, workstation, mainframe platform) ○ Number of computers on which data will be stored or analyzed ○ Whether personal computers used in the research project will be attached to a network or will operate independently (stand-alone)
    - Physical environment in which computer is kept (e.g., in room with public access, in room locked when not in use by research staff)
4. List and describe how data will be stored: (e.g., on PC hard drive, on removable storage media such as CD, diskettes, or Zip(R) drive.)
5. Describe methods of data storage when data are not being used.
6. Describe methods of transmitting the data between research team members (if applicable).
7. Describe methods of storage of computer output (in electronic form as well as on paper).

Types of protection expected: Although there are alternative ways to assure security for the data and applicants should prepare their plans in a manner that best meets their needs, some or all of the following features are typically found in successful data protection plans:

- Password protection for all files containing data (note that password protection is not regarded as sufficient protection by itself)

- Removable storage media holding the data (e.g., CDs, diskettes, zip disks, etc.) kept in a locked compartment/room when not in use
- Stored in a locked compartment/room when not in use
- No transmittal of data or analysis output derived from the data via e-mail, e-mail attachments, or FTP (either over the Internet, an Intranet system, or within a local area network)
- No backup copies of the data to be made
- Data stored in strongly encrypted form

Wherefore, **User** and Responsible Party hereby accepts responsibility for ensuring that the precautions formulated in their Data Protection Plan will be followed by signing and providing the information below:

Name (printed): Scott Carvajal

Signature: 

Institution: University of Arizona

Mailing Address: 1295 N. Martin Ave. PO Box 245209

Tucson, AZ 85724

Email Address: scott.carvajal@arizona.edu

Date: Oct. 15, 2018

Questions and/or completed data protection plans with **original signatures** should be emailed along with DUA and IRB to icpsr-nacda@umich.edu.

National Social Life, Health and Aging Project

This data use agreement is between **ICPSR** and the individual signing the agreement, hereafter referred to as **User**.

Whereas, the **NSHAP** data contain certain information **User** wishes to use for research, public health, or health care operations as permitted under 42 C.F.R. 164.514(e), **User** agrees as follows:

a. Not to use or further disclose the Limited Use **NSHAP** Data Set or any information contained therein other than as permitted by this agreement or required by applicable law.

b. To use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this agreement.

c. To report to ICPSR any use or disclosure of the Limited Use **NSHAP** Data Set or any part of it not provided for by this agreement of which **User** becomes aware.

d. Not to use the information contained in the Limited Use **NSHAP** Data Set to identify the individual whose information is contained in the Limited Use **NSHAP** Data Set, nor to contact them under any circumstances.

e. In the event **ICPSR** becomes aware of any use of the Limited Use **NSHAP** Data Set or any part of it that is not authorized under this agreement or required by applicable law, it may (i) terminate this agreement upon notice; (ii) disqualify the **User** from receiving protected health information in the future; and/ or (iii) report the inappropriate use or disclosure to the Secretary of the Department of Health and Human Affairs. Further sanctions may apply under 42 C.F.R. parts 160 and 164.

ICPSR and the **NACDA** Program on Aging will use the **User** information to create a registry to be used for quality assurance, bench marking and research follow-up with appropriate permission and in accordance with the requirements of the "Common Rule" 45 CFR 46 and the Privacy regulations 45 CFR 160 and 164.

The **User** agrees to provide **ICPSR** with information regarding the use of the **NSHAP** data for publications, seminars, conference papers, and other research related outcomes to be added in the bibliography of use that **ICPSR** maintains for all studies in its collections.

The Responsible Party **User** or PI proposing or supporting the use of the **NSHAP** data for research, must be a faculty level PI, a Research Scientist or have a similar full time appointment at a University, College or Research Center. Graduate students interested in using **NSHAP** for thesis development or research purposes must obtain the signature of their faculty advisor as the responsible Party **User**.

The **NSHAP** data must be maintained in a secure location. No duplication of the data for further distribution is allowed under this agreement. The data can not be placed upon an unsecured computer network for analysis.

Wherefore, **User** and Responsible Party hereby accepts and agrees to these terms by signing and providing the information below.

Name (printed): Scott Carvajal

Signature: 

Institution: Univeristy of Arizona

Mailing Address: 1295 N. Martin Ave., PO Pox 245209

Tucson, Arizona 85724

Email Address: scott.carvajal@arizona.edu

Date: Oct. 15, 2018

The following individuals (the "Authorized Parties") are authorized by the Responsible Party **User** to use the Limited Use **NSHAP** Data Set or any part of it on behalf of **UM** or **USER** and agree to abide by the terms of this Agreement:

Name: Rachel Peterson Signature: 

Name: _____ Signature: _____

Name: _____ Signature: _____

Completed form with **original signatures** should be emailed to icpsr-nacda@umich.edu.

NSHAP Data Protection Plan

Title of Research Project: Linking cumulative inequality theory to Alzheimer's disease disparities: A test of social and biological mechanisms

Principal Investigator(s): Scott Carvajal, PhD (Faculty advisor); Rachel Peterson (PhD Student)

Describe the computing environment in which the data will be used:
- **Computing platform:** PC
- **Number of computers on which data will be stored or analyzed:** 1

- **Whether personal computers used in the research project will be attached to a network or will operate independently (stand-alone):** The PC used for this research are part of the University of Arizona College of Medicine Network.

- **Physical environment in which computer is kept (e.g., in room with public access, in room locked when not in use by research staff):** The computer with access to the data is located in a private office at the University of Arizona Center on Aging. The UA Center on Aging offices are locked during non-business hours. No public access is granted to the computer workstation where data will be analyzed. Accessing the data files will require UA College of Medicine login credentials specific to Ms. Peterson.

List and describe how data will be stored:
Raw data received from ICPSR will be loaded onto the PC hard drives of one computer located at the University of Arizona Center on Aging offices.

Describe methods of storage of computer output (in electronic form as well as on paper).
Any data output created during analysis that contains data listings or unanalyzed data will be stored on the PC hard drive until analysis is complete. Note that this provision does not apply to fully analyzed data output (e.g. output from regression analyses, etc.)

Describe methods of transmitting the data between research team members (if applicable).
Only fully analyzed data (e.g. output from regression analyses, etc.), will be transmitted between research members.

Describe methods of data storage when data are not being used.
When data analyses pertaining to NSHAP data are inactive, all data files will be moved from PC hard drive to one or more password-protected flash drives, as needed, and stored in a locked filing cabinet at the University of Arizona Center on Aging offices.

Wherefore, User and Responsible Party hereby accepts responsibility for ensuring that the precautions formulated in their Data Protection Plan will be followed by signing and providing the information below:

Name (printed): Scott Carvajal **Signature:** 

Institution: University of Arizona
Mailing Address: 1295 N. Martin Avenue
Campus PO Box: 245209
Drachman Hall A254
Tucson, AZ 85724

Email Address: scott.carvajal@arizona.edu

Date: Oct. 11, 2018

APPENDIX D: IRB DOCUMENTATION

THE UNIVERSITY OF ARIZONA Research, Discovery & Innovation

Determination of Human Research

This form should be used when it is unclear whether the proposed activities require review by an Institutional Review Board (IRB). **If the proposed study clearly is Human Research, do not complete this form! Instead, please submit the appropriate application for review and approval by the IRB.**

Title (If funded, provide exact title of funded project)

Linking cumulative inequality theory to Alzheimer's disease disparities: A test of social and biological mechanisms

Contact Information

Principal Investigator Name	Rachel Peterson
Net ID	rachelpeterson
Email Address	rpeterson@aging.arizona.edu
College/Division	Public Health
Department/ Unit	Health Promotion Sciences

Status ☐ Undergraduate Student ☒ Graduate Student ☐ Resident ☐ Faculty ☐ Staff

Additional Contact (These individuals will receive copies of this correspondence):

Add Line	Name	UA Net ID	Research Role	Institution	Email Address
Delete Line					

Funding Information

Will the project be using/receiving any of the following funding types to support the research:

☒ No funding supporting the proposed research

☐ Federal funding (e.g., NIH, NSF, DoE, DoD)

☐ Foundation Funding

☐ Departmental Funds

☐ Gift Funds

☐ Industry Funded

THE UNIVERSITY OF ARIZONA Research, Discovery & Innovation

Determination of Human Research

Determination of "Research"

45 CFR 46.102(l): ***Research*** - a ***systematic investigation***, including research development, testing and evaluation, ***designed to develop or contribute to generalizable knowledge***.

A ***systematic*** approach involves a predetermined system, method or a plan for studying a specific topic, answering a specific question, testing a specific hypothesis, or developing theory. A systematic approach includes the collection of information and/or biospecimens, and analysis either quantitative or qualitative.

Activities ***designed to develop or contribute to generalizable knowledge*** are those activities designed to draw general conclusions, inform policy, or generalize outcomes beyond the specific group, entity, or institution (i.e., to elaborate, to be an important factor in identifying or expanding truths, facts, information that are universally applicable).

1. Does the proposed activity involve a ***systematic*** *approach*?

☒ Yes

☐ No

2. Is the intent of the proposed activity to ***develop or contribute to generalizable knowledge?***

☒ Yes

☐ No

If Yes to BOTH questions the study is Research. Proceed to *Determination of "Human Subject."*

If the answers to one or both questions are NO, proceed to *Determination of "Human Subjects" per FDA Regulations.*

Determination of "Human Subject"

45 CFR 46.102(e): ***Human subject*** - a *living individual* about whom an investigator (whether faculty, student, or staff) conducting research obtains: **(1)** data through ***intervention*** *or* ***interaction*** with the individual; or **(2)** ***identifiable private information***.

Intervention includes both physical procedures by which information is gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record information). Private information must be individually identifiable.

Identifiable is where the identity of the subject is or may be ascertained by the researcher, or will be associated with the information. The research could involve the use of ***coded*** data/specimens.

1. Does the activity involve obtaining information about *living individuals* through ***intervention*** or ***interaction*** with the individuals?

☐ Yes

☒ No

2. Does the activity involve obtaining ***identifiable*** and ***private information*** about living individuals?

☐ Yes

THE UNIVERSITY OF ARIZONA Research, Discovery & Innovation

Determination of Human Research

☒ No

If YES to either question, the research activity is *research* that involves *human subjects*. STOP and submit an IRB application for approval of human research.

If the answers to one or both questions are NO, proceed to *Determination of "Human Subjects" per FDA Regulations.*

Determination of "Human Subject" per FDA Regulations

21 CFR 50.3(g): *Human subject* - *an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.*

**Test article* means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation.

***In vitro diagnostic products* are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae.*

1. This is a clinical investigation involving a test article including in vitro diagnostics with a human subject(s) or their biospecimens?

☐ Yes

☒ No

Note: The FDA regulations (21 CFR Parts 50 and 56) apply to all clinical investigations regulated by FDA, as well as other clinical investigations that support applications for research or marketing permits. Therefore, all studies of investigational IVDs that will support applications to FDA are subject to 21 CFR Parts 50 and 56, even if they are not subject to most requirements of 21 CFR Part 812. For more information see the FDA Guidance on **In Vitro Diagnostic Device Studies - FAQs**.

Coded private information and/or human biological specimens per OHRP

Coded means a living individual's identifiable information such as name or social security number has been replaced by a code, such as a number, letter, or combination thereof ***and*** there is a key to link the code to the identifiable information of that individual. *Coded data are considered identifiable under the Common Rule.*

1. Does the activity involve the use of ***coded*** private information/specimens?

☒ Yes

☐ No

The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information /specimens pertain because:

☐ Yes ☒ No **a.** The holder of the key and investigator enter into an agreement prohibiting the release of the key to the investigator under any circumstances, until the individuals are deceased. **Provide a copy of this agreement (an informal email exchange is sufficient).** ***OR***

☒ Yes ☐ No **b.** The investigator has documentation of written policies and operating procedures from a repository or data management center that prohibits the release of the key to the investigators under any circumstances, until the individuals are deceased. **Provide documentation of the written policies and operating procedures.** ***OR***

☐ Yes ☒ No **c.** There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased. **Provide documentation of the legal requirements.**

2. Were the information/specimens previously collected (or yet to be collected), specifically for the currently proposed project?

☐ Yes
☒ No

Other Activities **(Please pick the most appropriate check boxes below)**
☐ **Program Evaluation/Quality Improvement/Quality Assurance:** The proposed activity will assess, analyze, critique, and improve current processes of program or health care delivery in an institutional setting, involving data-guided, systematic activities designed to bring about prompt improvements in a program or health care delivery?
☐ **Course-Related Activities**: The proposed activity is limited to course-related activities designed specifically for educational or teaching purposes?
☐ **Case Report:** The proposed activity is a case report or case series of no more than three (3) cases describing an interesting treatment, presentation, or outcomes?
☐ **Oral History:** The activity is limited to oral history activities, such as open ended interviews that only document a specific historical event or the experiences of individuals without the intent to draw conclusions or generalize findings.
☐ **Public Use Datasets:** The activity is limited to analyzing information contained within a publically available dataset (Meaning, any person can find and use the data). *NOTE: This does not include reviewing or analyzing information from social media.*
☐ **Journalism/Documentary Activities:** The activities are limited to investigations and interviews that focus on specific events, views, etc., and that lead to publication in any medium (including electronic), documentary production, or are part of training that is explicitly linked to journalism. There is no intent to test a hypothesis?
☐ **Purchased cell lines:** The activity involves commercially available, de-identified non-human embryonic cell lines.
☐ **Limited Data Set:** A limited data set is a data set that is stripped of certain direct identifiers specified in the Privacy Rule. A limited data set may be disclosed to an outside party without a patient's authorization only if certain conditions are met. Please go to the following link to review the Use Agreement (DUA) from the HIPAA Privacy Program
☐ **dbGap**: Receipt of data from dbGap that requires IRB approval, but the data you will receive. Investigators must also submit an Institutional Certification form to be completed and signed by the Investigator and IRB.
☐ **Preparatory to Research:** The activities are limited review of protected health information (PHI). No PHI is to be removed from the covered entity by the researcher in the course of the review.
☐ **PHI of Decedents:** The use or disclosure is solely for research on the PHI of decedent, the PHI is necessary for research purposes and if requested the Principal Investigator will be required to provide documentation of the death of the individual(s).
☐ **Native American/Alaskan Native**: The activity involves access to tribal resources (e.g. cultural artifacts, environmental samples, or people), but the activity is not intended to produce generalizable knowledge. Please attach a copy of completed Appendix for Vulnerable Populations.

Section 2: Summary

1. Provide a concise description of the purpose or objectives of the project.

The proposed research objective is to advance the understanding of drivers for Alzheimer's disease disparities by clarifying the relationships and pathways between social and structural determinants, potential modifiable risks, and biological mechanisms for cognitive function and rate of decline in older adults.

Using data from the National Social Life, Health and Aging Project cohort, a nationally representative longitudinal data set collected by researchers at the University of Chicago, I will explore how self reported experiences with inequality and adversity across the life course predict allostatic load (a biological indicator of chronic stress),

cognitive impairment and cognitive change.

2. Describe the proposed methods and study procedures.

Data will be statistically analyzed using regression and structural equation modeling techniques in Stata 14 and Mplus 7.

3. Describe the subject population, or the type of information/specimens to be studied.

Participants of the National Social Life, Health and Aging Project are older adults with over-sampling of race and ethnic minorities. Data collection started in 2005 and is ongoing every 5 years. I will be using data from all three waves currently available.

Allostatic load (biological markers of chronic stress) data were collected by researchers through standard height, weight and blood pressure measurement, and collection of saliva and blood samples. The data set also includes a variety of self-reported measures collected through surveys and interviews regarding perceived stress, childhood adversity and social support. Cognition was assessed with the Chicago Cognitive Function Measure (CCFM), a cognitive screening developed by NSHAP researchers for this study that is an adaptation of the Montreal Cognitive Assessment (MoCA).

4. Explain where the information/specimens were collected/obtained (i.e. identify source of data/specimens).

☐ NA- Activity does not involve the use of data/specimens
☐ Banner University Medical Center- Medical Records
☐ Data Warehouse
☒ Other

Are they a Business Associate or Collaborator?
Business Associate means a person or entity that performs certain activities or functions that involve the use or disclosure of PHI on behalf of, or provide services to, a Covered Entity.

☐ Yes
☒ No

Explain how the information/specimens will be provided to the investigator (e.g. the investigator will be provided an already existing, de-identified data set, etc.).

The investigator will be provided an existing, de-identified data set.

Section 3: Location of Research

☐ Banner - University Medical Center
☐ University of Arizona Cancer Center
☐ University of Arizona Campus
☐ Outside the U.S.
☐ Online
☒ Other

THE UNIVERSITY OF ARIZONA Research, Discovery & Innovation

Determination of Human Research

Data was collected by University of Chicago researchers from a nationally representative sample of older adults.

You have now completed this form. Next steps:

1) Please save a copy of this document for your records.

2) Email the form to the appropriate individuals for their approval.

3) Once it is ready email the application and attach all additional documents to vpr-irb@email.arizona.edu. Please review HSPP Guidance for any additional documents that are needed.

Principal Investigator

I certify that the information I provide in this application is correct and complete.

☒ Attestation of Principal Investigator

Rachel L. Peterson — Typed Name of Principal Investigator

1 Oct. 2018 — Date

NOTE: A research proposal by a graduate or undergraduate student must have the following attestation statement signed by an Advisor or Mentor.

Advisor/ Mentor

By signing below, I, the Advisor/ Mentor, certify that I have accurately reviewed and mentored the student/resident regarding completion of the items listed above.

Signature of Faculty Supervisor

10/4/18 — Date

Scott Carvajal, PhD, Professor Health Behavior Health Promotion

Print Name and Title of Faculty Supervisor

NOTE: Actual signature is not required. The HSPP Office will accept either email confirmation or an actual signature. This means that all signatures might not be on the same document. Attach email confirmations with your submission.

THE UNIVERSITY OF ARIZONA
Research, Discovery & Innovation

Human Subjects Protection Program

1618 E. Helen St.
P.O.Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://rgw.arizona.edu/compliance/home

Date:	October 07, 2018
Principal Investigator:	Rachel Peterson
Protocol Number:	1810994762
Protocol Title:	Linking cumulative inequality theory to Alzheimer's disease disparities: A test of social and biological mechanisms
Determination:	Human Subjects Review not Required

Documents Reviewed Concurrently:

HSPP Forms/Correspondence: *Peterson Determination of HSR 4 Oct. 2018.pdf*
HSPP Forms/Correspondence: *Peterson Determination of HSR 4 Oct. 2018 - signature page.pdf*
Other: *Peterson.Terms of use for NSHAP from ICPSR.docx*

Regulatory Determinations/Comments:

- Not Human Subjects Research as defined by 45 CFR 46.102(e): as presented, the activities described above do not meet the definition of research involving human subjects as cited in the regulations issued by the U.S. Department of Health and Human Services which state that "Human subject means a living individual about whom an investigator (whether professional or student)conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. "

The project listed above does not require oversight by the University of Arizona.

If the nature of the project changes, submit a new determination form to the Human Subjects Protection Program (HSPP) for reassessment. Changes include addition of research with children, specimen collection, participant observation, prospective collection of data when the study was previously retrospective in nature, and broadening the scope or nature of the study activity. Please contact the HSPP to consult on whether the proposed changes need further review.

The University of Arizona maintains a Federalwide Assurance with the Office for Human Research Protections (FWA #00004218).

APPENDIX E: STUDY MEASURES

Behavioral Risk Factor Surveillance System Measures

Module 7: Cognitive Decline

CATI NOTE: If respondent is 45 years of age or older continue, else go to next module

Introduction: The next few questions ask about difficulties in thinking or remembering that can make a big difference in everyday activities. This does not refer to occasionally forgetting your keys or the name of someone you recently met, which is normal. This refers to confusion or memory loss that is happening more often or getting worse, such as forgetting how to do things you've always done or forgetting things that you would normally know. We want to know how these difficulties impact you.

1. During the past 12 months, have you experienced confusion or memory loss that is happening more often or is getting worse? (376)

1 Yes
2 No **[Go to next module]**
7 Don't know **[Go to Q2]**
9 Refused **[Go to next module]**

Section 8: Demographics

8.7 What is the highest grade or year of school you completed? (158)

Read only if necessary:

1 Never attended school or only attended kindergarten
2 Grades 1 through 8 (Elementary)
3 Grades 9 through 11 (Some high school)
4 Grade 12 or GED (High school graduate)
5 College 1 year to 3 years (Some college or technical school)
6 College 4 years or more (College graduate)

8.8 Do you own or rent your home? (159)

1 Own
2 Rent
3 Other arrangement
7 Don't know / Not sure
9 Refused

INTERVIEWER NOTE: "Other arrangement" may include group home, staying with friends or family without paying rent.

NOTE: Home is defined as the place where you live most of the time/the majority of the year.

8.17 Is your annual household income from all sources— (175-176)

If respondent refuses at ANY income level, code '99' (Refused)

Read only if necessary:

0 4	Less than $25,000 ($20,000 to less than $25,000)	**If "no," ask 05; if "yes," ask 03**
0 3	Less than $20,000 ($15,000 to less than $20,000)	**If "no," code 04; if "yes," ask 02**
0 2	Less than $15,000 ($10,000 to less than $15,000)	**If "no," code 03; if "yes," ask 01**
0 1	Less than $10,000	**If "no," code 02**
0 5	Less than $35,000 ($25,000 to less than $35,000)	**If "no," ask 06**
0 6	Less than $50,000 ($35,000 to less than $50,000)	**If "no," ask 07**
0 7	Less than $75,000 ($50,000 to less than $75,000)	**If "no," code 08**
0 8	$75,000 or more	

Do not read:

7 7	Don't know / Not sure
9 9	Refused

National Social Life Health and Aging Project Measures

MEASURES USED FOR GLOBAL COGNITION SUMMARY SCORE

MOCA_MONTH2: moca 1: month correct?

The next questions are about problem solving and memory. The questions may seem unusual, but they are routine questions we ask everyone. Some of the questions are very easy and some are difficult, so don't be surprised if you have trouble with some of them. Try your best to answer all of the questions without using clues from around the room. If you wear glasses for reading, please use them.

Tell me the date today. First, tell me the month.

Value	Label
0	incorrect
1	correct
Missing Data	
-2	don't know

MOCA_DATE2: moca 2: date correct?

Now, tell me the exact date.

Value	Label
0	incorrect
1	correct
Missing Data	
-2	don't know

MOCA_RHINO: moca 3: rhinocerous

Now, I want you to name this animal. SHOW PICTURE #1 IN ALL-IN-ONE BOOKLET

Value	Label
0	rhino/rhinoceros
1	other (specify)
Missing Data	
-2	don't know
-1	refused

MOCA_CLOCK: moca items 4-6: clock administered

The next few things I will ask you to do are pencil and paper tasks. PLACE BLANK CLOCK PAPER FROM ALL-IN-ONE BOOKLET AND PEN BEFORE RESPONDENT. Now, I'd like you to draw a clock. Put in all the numbers and set the time to 10 after 11. (PROMPT IF NECESSARY: Try your best to complete this task without using clues from around the room, such as a clock or watch.)

Note: 1. some cases where moca_clock!=1 scored correct (see moca_contour, moca_numbers and moca_hands)
2. analysts may wish to score clock items as incorrect if moca_flag==9

Value	Label
1	completed task
2	completed task, but looked at clock or watch
3	tried, unable to do
4	r unable to understand instructions
Missing Data	

-1 refused

MOCA_CONTOUR: moca 4: clock contour score

moca 4: clock contour score
Skip if: MOCA_CLOCK equals "refused"

Value	Label
0	incorrect
1	correct
Missing Data	
-2	don't know

MOCA_HANDS: moca 5: clock hands score

moca 5: clock hands score
Skip if: MOCA_CLOCK equals "refused"

MOCA_NUMBERS: moca 6: clock numbers score

moca 6: clock numbers score
Skip if: MOCA_CLOCK equals "refused"

Value	Label
0	incorrect
1	correct
Missing Data	
-2	don't know

MOCA_TRAIL: moca 7: trails administered

PLACE TRAIL PAPER FROM ALL-IN-ONE BOOKLET AND PEN BEFORE RESPONDENT. Take a minute to look over the paper. Notice, there are both numbers and letters. Please draw a line, going from a number to a letter in increasing order. Begin here (POINT TO 1), and draw a line from 1 to A, then from A to 2, and so on. End here (POINT TO E). The first two lines have been drawn for you.

Value	Label
1	completed task
2	tried, unable to do
3	r unable to understand instructions
Missing Data	
-1	refused

MOCA_TRAIL2: moca 7: trails score

moca 7: trails score
Skip if: MOCA_TRAIL equals "refused"

Value	Label
0	incorrect
1	correct
Missing Data	
-2	don't know

MOCA_IR1_FACE: moca: immediate recall 'face'

This next section tests your memory. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them. Ready? READ SLOWLY (AT A RATE OF 1 WORD PER SECOND) AND PRONOUNCE CLEARLY: Face, Velvet, Church, Daisy, Red

Value	Label
1	repeated
2	did not repeat

MOCA_IR1_VELVET: moca: immediate recall 'velvet'

Value	Label
1	repeated
2	did not repeat

MOCA_IR1_CHURCH: moca: immediate recall 'church'

Value	Label
1	repeated
2	did not repeat

MOCA_IR1_DAISY: moca: immediate recall 'daisy'

Value	Label
1	repeated
2	did not repeat

MOCA_IR1_RED: moca: immediate recall 'red'

Value	Label
1	repeated
2	did not repeat

MOCA_5NUMBERS: moca 8: forward sequence (5 numbers)

Now, I am going to say some numbers and when I am through, repeat them to me exactly as I said them. READ THE FIVE NUMBER SEQUENCE TO THE RESPONDENT AT A RATE OF ONE DIGIT PER SECOND.
2, 1, 8, 5, 4

Value	Label
1	correct answer
2	incorrect answer
3	tried, unable to do
4	r unable to understand instructions
Missing Data	
-1	refused

MOCA_3NUMBERS: moca 9: backward sequence (3 numbers)

Now I am going to say some more numbers, but when I am through, I want you to repeat them to me in the backwards order. READ THE THREE NUMBER SEQUENCE TO THE RESPONDENT AT A RATE OF ONE DIGIT
PER SECOND.

7, 4, 2

Value	Label
1	correct answer
2	incorrect answer
3	tried, unable to do
4	r unable to understand instructions
Missing Data	
-1	refused

MOCA_SUBTRACT: moca 10: serial 7s (# correct)

Now, starting with 100, I would like you to subtract 7, and then keep counting down by 7.
(YOU CAN REPEAT THESE INSTRUCTIONS IF NECESSARY)

Value	Label
0	0
1	1
2	2
3	3
4	4
5	5
Missing Data	
-1	refused

MOCA_SENTCAT: moca 11: repeat sentence containing 'cat'

I am going to read you a sentence. Repeat it after me, exactly as I say it. (PAUSE) READ SENTENCE: The cat always hid under the couch when dogs were in the room.

Value	Label
1	correct answer
2	incorrect answer
3	tried, unable to do
4	r unable to understand instructions
Missing Data	
-1	refused

MOCA_WORD: moca 12: words that start with 'f'

Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns and names like Bob or Boston, and numbers or words that begin with the same sound, but have a different ending, for example, love, lover, loving. I will tell you to stop after 1 minute.
I will record your answers in this booklet. Are you ready? WHEN R IS READY: Now, tell me as many words as you can think of that begin with the letter F.

Note: 1. analysts may wish to score verbal fluency as incorrect if moca_flag==10
2. a correct score requires 11 or more words

Value	Label
1	correct answer
2	incorrect answer
Missing Data	
-6	missing in error
-4	no answer
-3	not applicable

MOCA_ALIKE2: moca 13: how are ruler and watch alike?

For this exercise, tell me what this pair of words has in common. Tell me how a ruler and watch are alike.

Value	Label
1	measuring instruments
2	used to measure
3	they have numbers
4	other (specify)
Missing Data	
-2	don't know
-1	refused

I read a list of words to you earlier, which I asked you to repeat and remember. Tell me as many of those words as you can remember. It doesn't matter in what order you say them.

MOCA_FACE: moca 14: delayed recall 'face'

Value	Label
1	repeated
2	did not repeat

MOCA_VELVET: moca 15: delayed recall 'velvet'

Value	Label
1	repeated
2	did not repeat

MOCA_CHURCH: moca 16: delayed recall 'church'

Value	Label
1	repeated
2	did not repeat

MOCA_DAISY: moca 17: delayed recall 'daisy'

Value	Label
1	repeated
2	did not repeat

MOCA_RED: moca 18: delayed recall 'red'

Value	Label
1	repeated
2	did not repeat

MEASURES USED FOR PERCEIVED STRESS SUMMARY SCORE

Now we will ask you about thoughts and feelings you may have had during the past week. How often during the past week you felt like this; rarely or none of the time, some of the time, occasionally, or most of the time? Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response

UNCNTRL: pss: unable to control important things

During the past week I was unable to control important things in my life.

Value	Label
1	rarely or none of the time
2	some of the time
3	occasionally
4	most of the time
Missing Data	
-5	not returned
-4	no answer

CONFIDNT: pss: confident about my ability

During the past week I felt confident about my ability to handle personal problems.

Value	Label
1	rarely or none of the time
2	some of the time
3	occasionally
4	most of the time
Missing Data	
-5	not returned
-4	no answer

GOMYWAY: pss: things are going my way

During the past week I felt that things were going my way.

Value	Label
1	rarely or none of the time
2	some of the time
3	occasionally
4	most of the time
Missing Data	
-5	not returned
-4	no answer

PILEDIFF: pss: difficulties piling up

During the past week I felt that difficulties were piling up so high I could not overcome them.

Value	Label
1	rarely or none of the time
2	some of the time
3	occasionally
4	most of the time
Missing Data	
-5	not returned
-4	no answer

MEASURES USED FOR SUBJECTIVE SOCIAL STATUS, INCOME AND ASSETS

INCOME_1: HH income relative to people you know

Compared with most of the people you know personally, like your friends, family, neighbors, and work associates, would you say that your household income is far below average, below average, average, above average, or far above average?

Value	Label
1	far below average
2	below average
3	average
4	above average
5	far above average
Missing Data	
-5	not returned
-4	no answer
-2	don't know

INCOME_2: HH income relative to American families

Compared with American families in general, would you say that your household income is far below average, below average, average, above average, or far above average?

Value	Label
1	far below average
2	below average
3	average
4	above average
5	far above average
Missing Data	
-5	not returned
-4	no answer
-2	don't know

HEARN: household income (last year)

Now, I'd like to ask you about the income of your household. Altogether, what would you say was approximately the income of your household in [CURRENT YEAR MINUS 1] before taxes or deductions?

HSASSETS: total household assets

Now I'd like you to think about all of the assets of your household. These are things like your house (if you own it), your cars, other rental properties and businesses you own, and financial assets like savings accounts, stocks, bonds, mutual funds, and pensions. Altogether, how much would you say that amounted to, approximately, after accounting for the loans you might have to pay off?